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STUDIES IN NORMAL PREGNANCY — SERUM LIPIDS LIPOPROTEINS AND URIC ACID (II)

A Skryten P Johnson and A Gustafson

From the Departments of Obstetrics and Gynecology and Medicine I Sahlgrenska Hospital University of Gothenburgh Gothenburgh Sweden

bstract Three different series of healthy pregnant women ithout any history or symptoms of metabolic disorder ave been studied for serum lipids (cholesterol) tri y-erides and phospholipids) as well as for cholesterol and iglyceride content in lipoprotein fractions in the 1st 2nd id 3rd trimesters Two other series of non pregnant ealthy women previously studied for serum lipids are esented for comparison

In the 1st trimester serum cholesterol decreased ($p <$ 01) as compared to non pregnant values In the 2nd and d trimester all serum lipids increased successively with aximum values during 3rd trimester all serum lipids in eased successively with maximum values during 3rd tri iester The changes were most pronounced in serum tri lycerides

Among lipoproteins cholesterol content increased in all ra-tions during the 2nd trimester and was most pronounc d *in very low density lipoproteins* (VLDL) (in the 2nd tri nester by 78 per cent and in the 3rd trimester by an addi ional 94 per cent) The increase in triglycerides in the 1st nd 2nd trimester was most pronounced in infranatant LDL+HDL) while in the 3rd trimester the triglyceride ontent was more evenly distributed among infranatant and ipernatant (VLDL) at density 1 006 g/ml It is suggested iat the increase in triglycerides is due to increased liver syn iesis in the 1st and 2nd trimester concomitant with an en anced removal i e by increased lipoprotein lipase activity PLA) In the 3rd trimester however LPLA is possibly hibated by subclinical cholestatic changes in the liver caus g a maximum triglyceride accumulation preferentially ated in VLDL

In an earlier study dealing with serum lipid changes in diabetic pregnancy marked hyperlipidemia in the 3rd trimester was a characteristic feature (23) Further more elevated serum triglycerides in the mother appeared to be related to an increased birth weight of her infant

A long parallel study was needed in normal preg nancy to allow a comparison with the serum lipid variables in diabetes The aim of the present in vestigation was to study serum lipids and lipoprotein distribution in normal pregnancy

MATERIAL AND METHODS

Clinical material Three different series of healthy pregnant women consecutively selected from the Maternal Welfare Unit one series of non pregnant healthy women and one series of postpartum women consecutively selected from the department of Obstetrics were studied

Series I (1st trimester) Twenty pregnant women (mean age 24 4 range 14–40 years) with normal uncomplicated preg nancy were studied at 8–12 weks (mean 10 6 weeks) of gestation

Series II (2nd trimester) Twenty pregnant women (mean age 26 6 range 20–41 years) with normal uncomplicated pregnancy were studied at 20–24 weeks (mean 21 7 weeks) of gestation

Series III (3rd trimester) Seventeen pregnant women (mean

le I *Serum lipids (cholesterol triglycerides and phospholipids) and uric acid at different stages of normal gnancy 1st trimester = week 10 (range 8–12) of gestation 2nd trimester = week 22 (range 20–24) and 3rd nester = week 34 (range 32–36) Serum lipid data are given in mg/100 ml*

nester		1st	2nd	1st vs 2 nd	3rd	2nd vs 3rd
lesterol	Mean	173	223		247	N S
	SEM	6	9		10	
lycerides	Mean	64	101		164	
	SEM	5	6		12	
spholipids	Mean	181	237	*	284	
	SEM	6	9		11	
acid	Mean	2 55	2 43	N S	3 38	
	SEM	0 19	0 15		0 19	

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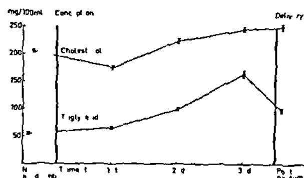


Fig 1 Serum lipids (cholesterol and triglycerides) at different stages of normal pregnancy in the non pregnant state and post partum 1st trimester = mean week 11 of gestation 2nd trimester = mean week 22 3rd trimester = mean week 34 and post partum = 2–5 days after delivery Number and age of patients see Material and Methods Data on serum lipids in mg/100 ml Mean±SEM

age 26 2 range 20–32 years) with normal uncomplicated pregnancy were studied at 32–36 weeks (mean 34 2 weeks) of gestation

Series IV (post partum) Ten normal post partum women (mean age 24 2 range 20–28 years (were studied 2–5 days after uncomplicated delivery following a normal pregnancy

Series V (non pregnant) Eighteen non pregnant women (*mean age 26 2 years range 19–34 years) with regular* menstrual cycles and not using oral contraceptives were *studied on the 1st or 2nd day of menstrual bleeding* and served as controls

The women in the five groups did not differ in mean age had a normal body weight and the pregnant women a normal weight gain throughout pregnancy Data in series III IV and V have partially been presented previously (20 21) and are only included for the purpose of comparison

Blood samples were drawn in the fasting state in the morning centrifuged at 2 500 × g for ten minutes and the serum thereafter immediately recovered frozen and stored at −20°C in glass tubes with teflon screw caps

Serum lipids Cholesterol was determined according to Cramer and Isaksson (5) triglycerides by the method of Carlson (4) and total phospholipids as described by Bartlett (1)

Serum lipoproteins Very low-density lipoproteins (VLDL) were isolated by ultracentrifugation

Centrifugation was carried out in a No 50 Rotor of the Spinco Model L Ultracentrifuge at 0 C for 22 hours at 105 000 × g The cholesterol (15) and triglyceride (4) content of supernatant and infranatant (D 1 006 g/ml) were determined The cholesterol content (15) of the α lipoproteins (α LP) was determined on whole serum after the elimination of VLDL and LDL by precipitation with heparin and manganese chloride (3) LDL cholesterol was estimated as the difference between cholesterol content of INF (infranatant) at density 1 006 g/ml and α lipoprotein (α LP) cholesterol

Uric acid was determined according to standard methods

Statistical methods Conventional methods were used for the calculation of means standard deviations and standard errors of means Student s t test was used to study differences between different groups and dependent t test was used *when analyzing differences between means within* groups When testing correlation coefficients between *different variables due consideration* was taken to the fact that some of them have a functional relationship (i e serum *cholesterol and its components*) Values of $p<0.05$ were considered statistically significant (2)

RESULTS

I Serum lipids in 1st trimester (Table I and Fig 1)

The present series of healthy pregnant women showed a decrease ($p<0.01$) in serum cholesterol in the 1st trimester as compared to non pregnant women

II Serum lipids in 2nd trimester (Table I and Fig 1)

All serum lipids cholesterol ($p<0.001$) triglycerides ($p<0.001$) and phospholipids ($p<0.001$) increased in the 2nd trimester as compared to the 1st

III Serum lipids in 3rd trimester (Table I and Fig 1)

Serum triglycerides ($p<0.001$) and phospho[lipids] ($p<0.01$) increased to reach a maximum value [in the] 3rd trimester as compared to the 2nd

IV Serum lipoproteins in 2nd trimester (Table **I and Fig 2)** Serum lipoproteins expressed as distribution among VLDL (very low density l

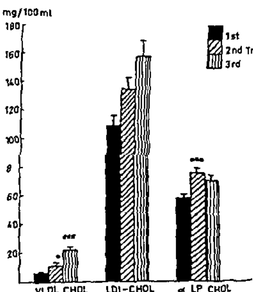


Fig 2 Cholesterol distribution among lipoproteins at different stages of normal pregnancy VLDL = very low density lipoproteins LDL = low-density lipoproteins α LP = α lipoproteins (*for isolation see text*) 1st trimester = mean week 11 of gestation *2nd trimester* = mean 22 3rd trimester = week 34 *Number and age of* Material and Methods Cholesterol content *mg/100 ml Mean±SEM*
*) = 0 05 **) = 0 01 ***) = 0 001 level

Table II *Lipoprotein triglyceride content at different stages of normal pregnancy Sup<1 006=very low density lipoproteins (VLDL) and inf>1 006=low-density lipoproteins (LDL) plus high density lipoproteins (HDL) 1st trimester=week 10 (range 8−12) of gestation 2nd trimester=week 22 (range 20−24) and 3rd trimester=week 34 (range 32−36) Triglyceride content is given as mg/100 ml Mean±SEM*

Trimester	1st	2nd	1st vs 2 nd	3rd	2nd vs 3rd
Triglyceride					
Sup<1 006 (VLDL)	29 0±3.2	41 5±5 5	N S	89 2±12 0	
Inf >1 006 (LDL+HDL)	44 0±3 7	65 7±4 4		92 4+5 1	*

0 05)0 01)0 001 level

ns) LDL (low density lipoproteins) and α LP lipoproteins) increased in the 2nd trimester as mpared to the 1st VLDL cholesterol increased by per cent ($p<0\ 01$) LDL cholesterol by 24 per cent $<0\ 05$) and α LP by 31 per cent ($p<0\ 001$) iglyceride content increased in the infranatant (INF 1 006 g/ml) *i e in LDL+HDL ($p<0\ 001$) in the* id trimester as compared to the 1st

Serum lipoproteins in 3rd trimester (Table II and g 2) Lipoprotein cholesterol content increased in LDL by 94 per cent ($p<0\ 001$) in the 3rd trimester compared to the 2nd Triglyceride content increas l in VLDL ($p<0\ 001$) and in LDL+HDL ($p<$ 001) in 3rd trimester as compared to the 2nd The tio LDL-triglyceride and α lipoprotein triglyceride as 2 1 (by weight) in the 3rd trimester

I Serum uric acid in the 1st 2nd and 3rd trimester Table I) Serum uric acid increased in the 3rd trimes r by 40 per cent ($p<0\ 001$) as compared to the 2nd imester

II Correlations between serum lipids and lipopro ins (Table III) Serum cholesterol was correlated to LDL cholesterol content in the 2nd trimester (r= 57 $p<0\ 01$) and to LDL cholesterol content in the t (r=0 93 $p<0\ 001$) 2nd (r=0 95 $p<0\ 001$) and d (r=0 93 $p<\leq 0\ 001$) trimesters Changes in LP-cholesterol did not influence serum cholesterol any major extent as judged from lack of correla on Changes in serum triglycerides mainly reflected ose in triglyceride content of VLDL as indicated by high correlation in the 1st (r=0 81) $p<0\ 01$) 2nd =0 84 *$p<0\ 001$) and 3rd trimester (r=0 64* <0 01) Serum triglyceride changes were related al ough to a lesser extent to triglyceride content in ranatant D 1 006 g/ml (LDL+HDL) in the 1st tri ester (r=0 64 $p<0\ 01$) and in the 2nd trimester =0 54 $p<0\ 05$) There was no correlation between um triglycerides and α LP cholesterol There was o lack of correlation between serum uric acid and um lipids

DISCUSSION

The present data in agreement with similar studies (6 14 24) reveal a marked elevation in serum lipids in normal pregnancy This increase in serum lipids was greatest in the later stages of pregnancy Cholesterol *increased were most pronounced in the 2nd trimester* and triglycerades and phospholipids in the 3rd Serum triglycerides increased by 200 per cent (as compared to non pregnant values) in the 3rd trimester After delivery serum triglycerides declined within a few days to approach non pregnant levels (Fig 1) Two to five days after delivery however both serum cholesterol and triglycerides were still higher ($p<0\ 01$) than in the non pregnant state

In the 2nd trimester the increase in serum cholesterol was due to an increase in cholesterol content of all lipoprotein fractions i e VLDL LDL and α LP This generalized cholesterol increase might be due to the effect on cholesterol metabolism either of increased synthesis or more likely of decreased catabolism Data on serum lecithin fatty acid composition (22) has been interpreted in the 2nd and 3rd trimester as indicating a subclinical cholestatic involvement of the liver The presence of increased bile acids in the liver in mild cholestasis would be expected to inhibit cholesterol catabolism (11) In the 1st trimester on the other hand a reduction in serum cholesterol might be the expression of an estrogen influence on liver metabolism since serum lecithin relative fatty acid composition in the 1st trimester would *indicate* an estrogen influence on liver lipid synthesis (22) Furthermore it has been well documented that the administration of estrogens in man decreases serum cholesterol (10 16 18)

Since serum triglyceride primarily reflect VLDL triglyceride content as judged by the high correlation in all trimesters it is suggested that increased triglyceride synthesis is the primary cause of elevated serum triglycerides during *pregnancy Increased tri*

Table III *Correlations (r values) between serum lipids and lipoprotein variables at different stages of norm pregnancy 1st trimester = week 10 (range 8–12) of gestation 2nd trimester = week 22 (range 20–24) and 3 trimester = week 34 (range 32–36)*

Trimester	1st	2nd	3rd
Serum CH vs VLDL CH	0 14	0 57	0 07
Serum CH vs LDL CH	0 93	0 95	0 93
Serum CH vs α LP CH	0 30	0 28	0 18
Serum TG vs VLDL TG	0 81	0 84	0 64
Serum TG vs (LDL + HDL) TG	0 64	0 54	0 43
Serum TG vs VLDL CH	0 14	0 88	0 90
Serum TG vs α LP CH	0 17	0 25	0 30

) 0 05) 0 01) 0 001 level

glyceride levels during pregnancy might be related to an increased level and turnover of free fatty acids (FFA) (7) to disturbances in carbohydrate metabo lism associated with an elevated basal insulin level (hyperinsulinemia) (17) as well as to elevated growth hormone (STH) concentration (19 9)

During early pregnancy an increased synthesis would possibly be compensated by an increased tri glyceride efflux by lipolysis and also by transfer of tri glycerides from VLDL to LDL In the 3rd trimester an elevated VLDL content of both cholesterol and triglycerides would possibly indicate that this efflux was partially inhibited A decreased efflux might among other things suggest a decreased lipoprotein lipase activity (LPLA) In view of the suggestion of a subclinical cholestatic condition in the 3rd trimester (22) an inhibition of LPLA by bile acids would be a possible explanation

A high triglyceride content in HLD (in the 3rd tri mester 20 per cent of total serum triglycerides were found in HLD) would suggest the appearance of tri glyceride rich associated or non associated lipopro tein families in HDL presumably LP C originating from the catabolism of VLDL An alternate explana tion for triglyceride rich HDL would be the ap pearance of abnormal LP A originating in the liver induced by an accentuated triglyceride (12 13) and protein synthesis (8) Studies in progress on the lipoprotein families of HDL will hopefully give an answer to this intriguing metabolic question

ACKNOWLEDGEMENTS

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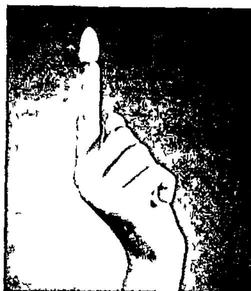
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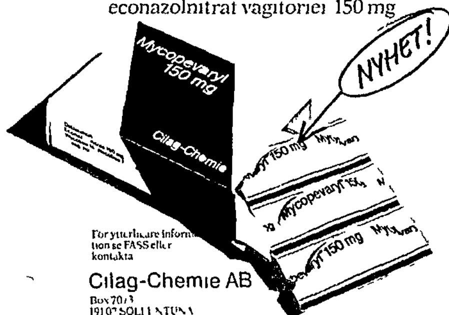


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INTERVILLOUS BLOOD FLOW IN NORMAL AND COMPLICATED LATE PREGNANCY MEASURED BY MEANS OF AN INTRAVENOUS ^{133}XE METHOD

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Abstract Intervillous blood flow (IVBF) was measured in ravenously with a new quantitative ^{133}Xe method in 50 normal and 74 complicated late pregnancies between the 15th and 42nd weeks The distribution of individual flow ates seemed to be fairly wide in both the normal and the pathological groups The mean rate of IVBF in normal pregnancies was 140 ml/100 ml of intervillous space/min he lowest mean flow values were observed in pregnancies omplicated by diabetes mellitus (class B-E) cholestasis of regnancy and severe pre-eclampsia a highly significant ifference ($p < 0\ 001$) from the mean IVBF observed in nor al pregnancies The significance of the results in the ifferent groups has been discussed in detail This method ay open up a new diagnostic area in the management of gh risk pregnancies

tervillous blood flow (IVBF) is important for fetal itrition respiration and excretion (4) and in normal egnancy it increases towards term (25) Changes in aternal hemodynamics and structural properties of placenta may markedly alter the IVBF (3 11 25) ie acute reduction of IVBF required to place the us at risk has been estimated to be fifty per cent) The reduced IVBF usually associated with intra rine hypoxia may result in growth retardation in injury and occasionally even death of the fetus 26)

Most of the radionucleide methods developed for evaluation of IVBF have the disadvantages they only qualitative information (5 16 25) Recent a new quantitative method for measuring IVBF presented (20) This method is based on intrave is use of ^{133}Xe In order to evaluate this new hod we studied IVBF in normal pregnancies and patients with some of the most common complica s of late pregnancy

MATERIAL AND METHODS

nts The series consisted of 124 pregnancies between 5th and 42nd gestational weeks The pregnancies were ed into six groups according to maternal diagnosis (Table I) The White classification was used in diabetes mellitus The case was considered one of dysmaturity if the weight of the newborn was under the 10th percentile and the pregnancy was otherwise normal (9) Fifty one of the preg nancies were studied in the University Central Hospital of Oulu and 93 in the Central Hospital of Central Finland in Jyväskylä Fifty of the pregnancies were normal and they were used as a control group

^{133}Xe method The placental site was localized in advance by means of ultrasonic B-scanning and only those with anterior wall placentas were included in the final series During the examination the patient lay in a 15 C left lateral tilted position The gamma camera head with a low-energy collimator (RADICAMERA) was placed over the placental area A dose of 2 5 mCi of ^{133}Xe saline (gamma radiation energy 80 keV half life 5 3 d) was injected rapidly into the left antecubital vein through a two-way syringe and flushed immediately with 10 ml of physiological saline To minimize the excretion of ^{133}Xe through the lungs the patient was told to hold her breath for 15 20 s after the injection For re cording quantitative data from the placenta a data storage (PDP 8 12 k words) and read-out system with fast televi sion techniques (NUKAB) was connected to the scintillation camera The data in digital form were collected using 64×64 image matrices with 10 s channel width over 10 minutes After the measurements were taken the data were transfer red onto a magnetic disc The total data density over the placenta ranged from 200 to 2 000 counts per cm^2 The peak count rate was 1 000- 10 000 counts/10 s The procedure us ed in Jyväskylä was the same with the exception that a func tion measurement system with two detectors was used The method was reported in detail previously (20)

Calculation The time activity curve of each area was fed off line into a central computer (NOVA 840 64 k words) for processing (in Jyväskylä the detectors were connected on line to a NOVA 1220 minicomputer) A two-exponential function ($A_1 \exp(k_1 t) + A_2 \exp(k_2 t)$) was fitted to the measured wash-out curve using the least square method The fast component describes the fractional removal ($dQ(t)/dt = k_1 Q(t)$) of the tracer from the intervillous blood pool The regional intervillous flow (in ml/100 ml/min) was calculated from the equation $F_1 = 100\ k_1$ and the myometrial flow from the slow component by using the conventional wash out equation $F_2 = p\ k_2$ where p is the partition coefficient between blood and myometrium (70 ml/100 g hematocrit 45 per cent) Myometrial blood flow was not recorded in this study

Radiation dose to fetus was less than 1 mrad

Table I *The rates of intervillous blood flow birth weights of infants and placental weights in normal (…) complicated pregnancies*

Diagnosis	N	Intervillous flow ml/100 ml/min		Infant birth weight (g)	Placental weight (g)
		mean±SD	range	mean±SD	mean±SD
Normal pregnancy	50	140±53	73–261	3 614±384	638±111
Essential hypertension	31	112±39	63–183	3 420±592	597±126
Severe pre-eclampsia	11	99±27	61–120	3 181±590	565±139
Diabetes mellitus (class A)	5	110±16	96–138	3 872±592	768±256
Diabetes mellitus (class B-E)	7	89±19	76–131	3 439±781	644±149
Cholestasis of pregnancy	8	94±14	66–114	3 350±425	600±92
Dysmaturity (<10th percentile)	12	109±34	64–164	2 482±537	440±101

= almost significant ≈ significant highly significant

RESULTS

The mean values standard deviations and ranges of IVBF infant birthweight and placental weight in normal cases and the different groups of complicated pregnancies are presented in Table I The mean IVBF was highest in normal pregnancies (140±53 ml/100 ml/min) and lowest in diabetes mellitus (class B E) (89±119 ml/100 ml/min) In essential hypertension the reduction of IVBF was almost significant ($p<0.05$) and in all the other groups significant ($p<0.01$) or highly significant ($p<0.001$) if compared with the mean value of the control group In severe pre eclampsia the mean birthweight was almost significantly ($p<0.05$) lower than in normal pregnancy and in dysmaturity the difference was of course highly significant ($p<0.001$) In the other groups there were no statistically significant weight differences

The percentage of dysmature babies (19) in the different groups were as follows normal pregnancy 6 essential hypertension 23 severe pre eclampsia 45 diabetes mellitus (class A) 0 diabetes mellitus (class B E 14 and cholestasis of pregnancy 25

Only in dysmaturity was the mean placental weight statistically lower than in normal pregnancies ($p<0.001$) The feto placental weight ratios were normal in all groups (17±2 per cent)

Seven of the infants had a 1 minute Apgar score of six or less while all the others were in good condition

We had one fetal loss in this series The mother was a 30-year old primigravida with diabetes mellitus (class E) and superimposed severe pre eclampsia IVBF on the 35th gestational week one week before the death was only 75 ml/100 ml/min The stillborn baby was very dysmature weighing 1 940 g

DISCUSSION

The mean IVBF determined by the present (…) can also be expressed as half life and appears to (…) *normal pregnancies* very similar to the value (…) ed by Dixon *et al* (8) who used to the (…) Na method The flow values measured by C(…) *al* (6) with their invasive ^{133}Xe method were (…) than ours however Gitsch and Janisch (11) (…) intravenous $^{99}Tc^{m}O_4$-method reported a value for IVBF almost identical to (…) difference being that they expressed the flow in (…) of placental tissue instead of 100 ml of (…) pool

The mean IVBF in *essential hypertension* (…) study was 112±39 ml/100 ml/min ($p<0.05$) in *severe preeclampsia* 99±27 ($p<0.001$) It (…) known that in pregnancies complicated by (…) hypertension or pre eclampsia the IVBF can (…) ously reduced Browne and Veall (3) in their pio(…) ing work found a reduction of 60 per cent in the (…) of patients with essential hypertension Suonio (…) reported also a significant decrease of trace(…) cumulation ($^{99}Tc^{m}O_4$) in pre eclampsia and ess(…) hypertension In pregnancies complicated by h(…) tension proteinuria or edema elevated uterine (…) (14) and constriction of the supplying arteries (…) result in diminished intervillous space perf(…) despite the elevated maternal blood pressure La(…) pregnancy morphological abnormalities may (…) vene and ultimately dominate the picture (…) clusive vascular lesions in decidual arteries have (…) shown to be a feature of hypertensive pregnan(…) 9 22 24) All these changes may result in a red(…) of the placental flow rate

According to our findings the mean IV(…)

abetes mellitus (class B E) was the lowest (89 100 ml/min) In milder diabetes (class A) the IVBF was of the same order as in essential hy ı or dysmaturity Gitsch and Janisch (11) .so reported a very low IVBF (31 per cent of the nor ı) for diabetes mellitus In severe diabetes mellitus the maternal hemodynamic factors and structural ıes of the vessels may be grossly altered The of hyperinsulinemia may result in acceler cell division and an increased placental cell size 11) This leads to a prolonged proliferation of cyto- syncytiotrophoblast and a failure of their at enuation during the second half of pregnancy The otal intervillous space volume may thus be con iderably reduced due to edema of the villi (1) which with other changes may lead to altered through the intervillous space It is pro- le that there is a good correlation between the :everity of the disease and the reduction of IVBF

'holestasis of pregnancy is associated with an elev ted perinatal mortality of unknown etiology (10 13 1 23) The mean IVBF in this group was almost as w as in the severe forms of diabetes mellitus (class E) No studies of placental hemodynamics in chole asis of pregnancy can be found in the literature and nce the mean value of IVBF (94/100 ml/min) now orded cannot be compared with others In chole sis of pregnancy however placental permeability certain amino acids is altered (28) Accordingly re may also be some differences in the diffusion of e into fetal circulation However this diffusions the fetal circulation is low even in normal cases loes not apreciably influence the results (17) It is nt that more studies are needed to explain the ntal hemodynamics found in cholestasis of ıancy

growth retardation is widely reported as the common consequence of impaired placental d flow (5 27) Our results do not strongly sup- this opinion The mean flow (109 ml/100 ml/ in this group was in fact significantly ($p<0\ 01$) r than in the normal group however it was not w as that found in the groups with severe pre-ec ısia and diabetes mellitus (class B-E) in which nfants were mostly (in 55 86 per cent) normal in ht Yet both Chatfield (5) and Suonio (25) using ıccumulation methods found that the placental ke of tracer in pregnancies resulting in growth re :d babies was significantly reduced Wolfson and e (27) using an inhalation method (^{133}Xe) also rted significantly longer half lives in pregnancies with growth retardation Crob *et al* (7) used the estimation of the placental blood flow for growth retardation babies to discriminate between a placental and an extraplacental origin of the disorder It is ob- vious that many of the dysmature babies in our study are growth retarded because of extraplacental e g genetic causes and this may explain the relatively moderate decrease in the mean IVBF

Our present findings indicate some new aspects of placental hemodynamics in complicated late pregnan cy A comparison of the results with earlier findings is not easy because of differences in methodology and quantification The disadvantages and benefits of our method have been discussed elsewhere (20) It can be regarded as a safe method for the fetus and the mother and therefore can be repeated in the follow up of high risk pregnancies

Although this method cannot yet be considered a routine clinical tool it seems to be of great value in the interpretation of the hemodynamic background of some high risk groups in late pregnancy The reproducibility of this method is about 20 ml/100 ml/min ($r=0\ 88$) Detailed flowmetric animal ex periments could give more accurate information on the value of this method in determining IVBF quan titatively

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WATER AND ION METABOLISM IN PLACENTA (III)

Net movement of water monovalent and divalent cations in slices from rabbit placenta at different periods of gestation incubated under metabolically favorable conditions

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Rabbit placenta slices incubated at 38 C in ox ·genated medium in the presence of endogenous substrates 5 mM glucose after a period of preincubation of 120 min 0–1 C *show a net accumulation of potassium and ex* ·usion of water sodium and calcium The movement of ota.sium sodium and calcium appears to be related to the ate of oxygen consumption of the slices and to be inversely onal to the age of the tissue The efficiency of ca movement is also dependent on the nature and com tion of the incubation medium In this respect the otassium concentration of the medium plays a major role he movement of water on the other hand seems to be mpletely independent from both the rate of respiration d the age of the tissue The results are discussed in terms relation between placenta age and senescence and effi ·ncy of the mechanisms devoted to the cell regulation of ter and ions content

preceeding papers of this series we have presented dence for the different water and ion composition placental tissue in relation to its age (2) together h the peculiar changes undergone by the tissue ter and ion gradients during incubation under tabolically unfavorable conditions (3) In this per we show the results of experiments performed h the aim of elucidating from a metabolic point of w the basic mechanisms of regulation of water l ion content in placenta slices incubated *in vitro* relation to the tissue age and senescence The ults obtained clearly show that placenta slices r a period of incubation at 0–1 C during which y reach a chemical equilibrium with the incubation dium (3) are indeed capable of regenerating ion dients across cell membrane and of extruding the ess of water previously gained

Moreover the efficiency of these processes which the other hand represent the reversible phase of ue and cell edema is strictly dependent on

(a) the nature of the incubating medium Rabbit plasma in fact appears more suitable in comparison with an artificial saline solution (Ringer Tris)

(b) The potassium content of the incubation medium Increasing up to 15 mM the concentration of plasma potassium in fact the recovery of ion gradients is more effective

(c) The rate of O_2 consumption of the tissue This parameter which gives a reliable idea of the energy state of the cell appears to be in turn related both to the age and senescence of placenta and to the incuba tion conditions

(d) The age and senescence of placental tissue Unlike water extrusion which is almost equally efficient in all the conditions tested the regeneration of ion gra dients especially those of sodium and potassium is 100–200 per cent more effective in the younger than in the beyond term placentae All these results will be discussed as evidence for the decreased effectiveness of basic physiological mechanisms meant to preserve cell homeostasis during placental growth and senescence Some observations on the proper incuba tion conditions for placental tissue will also be discussed

Table I *Inulin space (α inulin) in slices from rabbit placenta at different periods of gestation incubated in Ringer Tris or Plasma both at 0–1 C and 38 C*

Gest period	0–1 C Ringer Tris	0–1 C Plasma	38 C Ringer Tris	38 C Plasma
II	383 ± 01(16)	266 ± 03(9)	691 ± 021(9)	459 ± 01(9)
IV	363 ± 03 (6)	293 ± 03(6)	n d	460 ± 07(6)
V	383 ± 02 (9)	326 ± 05(3)	717 ± 1 (5)	.532 ± 04(5)

After equilibration slices inulin content has been determined on the perchloric acid extract following Kulka (Ref no 3)

Table II *Total water content and size of intra and extracellular water compartments in slices from rabb placenta at different periods of gestation incubated under metabolic favourable conditions (38 C) in differe suspending media after 120 min of preincubation at 0–1 C*

A Preincubation 120 min at 0–1 C

Period of gestation	Ringer Tris H_2O_{tot}	H_2O_i	H_2O_e	Plasma H_2O_{tot}	H_2O_i	H_2O_e	Plasma + 10 mM K+ H_2O_{tot}	H_2O_i	H_2O_e
II	6 8± 1 (45)	4 2	2 6	5 3± 06 (44)	3 7	1 6	5 3± 07 (8)	3 7	1 6
IV	6 4± 1 (18)	4 0	2 4	5 6± 06 (25)	3 9	1 7	5 7± 09 (8)	3 9	1 7
V	6 4± 1 (15)	4 0	2 4	5 6± 02 (18)	3 9	1 7	5 8± 04 (8)	3 9	1 7

*The size of intra and extracellular water compartments has been calculated on the basis of the spa e of inulin (mean value at 0-1 C and 38 C either in Ringer Tris or Plasma for the different periods of gestation (Table I)

B Incubation 60 min at 38 C after the preincubation

Period of gestation	Ringer Tris H_2O_{tot}	H_2O_i	H_2O_e	Plasma H_2O_{tot}	H_2O_i	H_2O_e	Plasma + 10 mM K+ H_2O_{tot}	H_2O_i	H
II	5 8± 1 (26)	1 7	4 1	4 4± 02 (44)	2 3	2 1	4 1± 01 (8)	2 1	2 0
IV	5 5± 09 (18)	1 6	3 9	4 6± 06 (25)	2 4	2 2	4 6± 03 (8)	2 4	2 2
V	5 5± 2 (12)	1 6	3 9	4 4+ 06 (18)	2 3	2 1	4 6± 03 (8)	2 4	2 2

MATERIAL AND METHODS

The methods followed in the present work are essentially the same as those described in the preceeding papers (2 3)

Rabbit pregnancy was arbitrarly subdivided into the usual *five periods (2) in this work however we restricted the* observation to three periods only period II (16th 20th day of gestation) period IV (26th 30th day of gestation) and *period V (31st 33rd day of gestation) To bring the* pregnancy to the period V animals were treated with *HCG* as already described (2) Placental slices cut free hand by *razor blade were kept for 120 min at 0–1 C in an ice bath* and suspended separately in each of the following media

1) Ringer Tris (158 mM Na^+ 5 mM K^+ 5 mM Ca^{2+} 1 0 mM Mg^{2+} 1 0 mM $SO^2{}_4$ 175 6 mM Cl and 10 mM Tris HCl pH 7 4)

2) rabbit plasma with the addition of 10 mM Tris HCl pH 7 4

3) rabbit plasma with the addition of 10 mM K^+ (KCl) and 10 mM Tris HCl pH 7 4 Rabbit plasma was obtained from the same pregnant animals by collecting the blood before the placenta was removed

After the cold preincubation the slices were transferred to Warburg vessels with a central well and incubated for 1 hour at 38 C in the presence of 5 mM glucose (added only to the artificial Ringer Tris) and of pure oxygen as gas phase During this period the O_2 uptake was determined by the Warburg method in the presence of 0 2 ml of 20 per cent KOH in the central well At the end of the incubation at 38 C the slices were carefully withdrawn gently blotted on hardened filter paper and placed in tared plastic screw cup bottles The wet and dry weight of the tissue and the ion content of the slices were determined as described before (2) In parallel experiments the space of inulin of the sli e was determined performing the incubation in the above-*mentioned media in the presence of 0 5 per cent* previously described (3) Sodium potassium calc magnesium were determined by atomic absorption trophotometry Deionized water (>20 mΩ) was throughout the work

RESULTS

The inulin space (α inulin) determined in slices f *rabbit placenta at different periods of gestation* cubated 120 min at 0–1 C and subsequently at 38 C both in Ringer Tris and plasma is in Table I The α inulin which gives a measure extracellular space is not significantly different slices *from the three gestation periods studied* also ref 3) but its mean value is about 25 per lower in the tissue suspended in plasma This is bably due to the different oncotic pressure of suspending media A substantial increase of α inulin of about 70 per cent can be *observed in* media when the slices are transferred from 0–1 38 C This indicates that a large change in distribution of water between intra and extrac compartments when active metabolic conditi restored occurs

Total tissue water content decreases at 38 *about 15–20 per* cent in all the condition regardless of both the incubation medium used the period of gestation (Table II)

III A Na$^+$ (mmol/kg d wt) movements in rabbit placenta slices at different periods of gestation in at 0–1 C and 38 C in Ringer Tris Plasma and 10 mM K$^+$ supplemented Plasma Effect of 1 mM n

of ation	0–1 C Ringer Tris	Plasma	Plasma + 10 mM K$^+$	38 C Ringer Tris	Plasma
II	985 4±21 8 (45)	886 0±15 6 (44)	787 4±21 3 (8)	959 4±45 5 (17)	687 0±34 4 (25)
IV	1044 0±57 4 (18)	894 5±14 6 (25)	804 0±39 1 (8)	934 8±70 9 (18)	719 4±25 7 (25)
V	945 5±28 0 (15)	842 5±24 6 (18)	837 5±28 6 (8)	897 0±39 0 (12)	786 8±19 7 (18)

able III A continuation

C (cont) Plasma + 10 mM K$^+$	Plasma + 1 mM oubain	Per cent recovery Ringer Tris	Plasma	Plasma + 10 mM K$^+$	Plasma + oubain
7±22 2 (8)	897 6±38 4 (4)	4 3	39 0	68 6	– 2 3
3±28 4 (8)	876 3±41 7 (4)	20 0	44 1	61 5	4 6
4±34 2 (8)	890 0±13 6 (4)	11 0	16 5	30 1	–14 0

The net extrusion of water from the slices together h the swelling of the interstitial compartment hich take place at 38°C cause a drastic shrinkage of e intracellular compartment From the data of ble II in fact it can be seen that at 38 C placental lls lower their water content by 40–60 per cent e expulsion of water takes place in all the suspen media The recovery can be considered complete ce the H_2O_i in some cases is even lower than in fresh tissue (2)

Table III summarizes the content of Na$^+$ and K$^+$ the placenta slices at different periods of gestation incubated in Ringer Tris plasma and plasma + 10 mM K$^+$ for 60 min at 38 C after the preincubation of 120 min at 0–1 C

In the last columns of the table the per cent recovery in each condition tested is also reported The slices incubated at 38 C in Ringer Tris expell and take up a small amount of Na$^+$ and K$^+$ respectively regardless of the period of gestation The per cent recovery in fact is only in this case in the range of 5–20 per cent

The activity can be stimulated by incubating the slices in rabbit plasma Na$^+$ extrusion in fact in

le III B K$^+$ (mmol/kg d wt) movements in rabbit placenta slices at different periods of gestation in ited at 0–1 C and 38 C in Ringer Tris Plasma and 10 mM K$^+$ –supplemented Plasma Effect of 1 mM n

of ation	0–1 C Ringer Tris	Plasma	Plasma + 10 mM K$^+$	38 C Ringer Tris	Plasma
I	184 8± 7 4 (45)	203 8±11 0 (44)	197 5±18 7 (8)	191 7±11 8 (17)	261 6±7 4 (25)
I	144 0± 6 1 (18)	127 4± 4 8 (25)	153 5±11 1 (8)	159 1± 5 5 (18)	152 6±3 7 (25)
I	133 2±12 6 (15)	143 2± 7 9 (18)	138 5±21 4 (8)	142 9±11 2 (12)	136 2±5 2 (18)

e III B continuation

(cont) Plasma + 10 mM K$^+$	Plasma + 1 mM oubain	Per cent recovery Ringer Tris	Plasma	Plasma + 10 mM K$^+$	Plasma + oubain
±34 3 (8)	103 0±9 3 (4)	2 0	18 2	64 8	–31 7
±24 5 (8)	59 3±4 2 (4)	5 3	8 2	42 1	22 4
±27 2 (8)	97 4±4 5 (4)	4 1	3 1	19 9	–20 4

r cent recovery has been calculated on the basis of the potassium content of the fresh tissue taken from Ref no 2

Table IV A *Sodium [$Na^+{}_i$(mM)] intracellular concentration of rabbit placenta slices at different periods of gestation incubated at 0–1 °C and 38 C in different suspending media*

Period of gestation	0–1 C Ringer Tris	0–1 C Plasma	0–1 C Plasma + 10 mMK+	38 C Ringer Tris	38 C Plasma	38 C Plasma + 10 mMK+
II	136 8	171 1	144 5	183 3	154 4	89 9
IV	166.2	160 5	137 3	199 2	154 9	111 5
V	141 6	147 2	145 9	175 5	197 8	162 4

creases to about 40 per cent in the slices of the period II and IV while it is still low (16 5 per cent) in those of period V As far as K+ is concerned the recovery is more pronounced and it also occurs in inverse relation to the age of placenta

These results show that placenta behaves quite differently from other tissues The extensive studies of van Rossum (4 8) indicate that slices from rat liver or from some neoplastic tissues are able to regain in the Na^+ K^+ and Ca^{2+} gradients when they are incubated at 38 C under suitable metabolic condition even when suspended in artificial saline solution

Preliminary experiments which showed that placenta slices incubated at 38°C in Ringer Tris but without the previous incubation at 0–1 C fail to regain ion gradients (results not shown) suggest that the cold incubation does not irreversibly spoil the tissue

We thought therefore that the discrepancy between liver and placenta might be related to some peculiar constituent of the incubating medium necessary for the placental tissue to keep *in vitro* the ion gradients exhibited *in vivo* (2)

Following this reasoning and knowing that
(a) in some systems membrane Na^+ K^+ ATPase is strongly dependent on the [K^+] outside the cell (see for review 6) and
(b) [K^+] in the fetal blood is higher than that in maternal blood (for review see 1) we increased the [K^+] of the rabbit plasma to 15 mM in an attempt to improve the active ion movements

Indeed we have found that placenta slices the most active Na^+ extrusion and K^+ they are incubated in rabbit plasma with added mM K^+ The recovery of the sodium now becomes of 68 6 61 5 and 30 1 per periods II IV and V respectively while the potassium increases to 64 8 42 1 and 19 9 per cent the three periods respectively

It is apparent that the placentae from the term pregnancies always show the lowest The regeneration of Na^+ and K^+ dients across the plasma membrane implies diture of energy utilized by a specific ATPase enzyme is known to be sensitive to the inhib bain which indeed inhibits also the placenta stimulated ATPase In the presence of 1 mM slices Na^+ in fact remains high and potassium and the recovery is completely lacking negative (Table III) From the knowledge of of intracellular water compartment and the tissue sodium and potassium it is calculate the intracellular concentration o Such data are reported in Table IV After incubation in the cold the concentration on side the placental cells is equal to that of the medium (see also ref 3) A concentration mM is found in the slices incubated both in Tris and plasma or plasma + 10 mM K^+ At despite the apparent recovery shown in Table intracellular concentration of Na^+ is still h Ringer Tris and in plasma Only when the sl

Table IV B *Potassium [$K^+{}_i$(mM)] intracellular concentration of rabbit placenta slices at different gestation incubated at 0–1 °C and 38 C in different suspending media*

Period of gestation	0–1 C Ringer Tris	0–1 C Plasma	0–1 C Plasma + 10 mMK+	38 C Ringer Tris	38 C Plasma	38 C Plasma + 10 mMK+
II	40 9	52 9	46 9	100 7	109 2	179 8
IV	33 0	30 5	39 3	87.3	59 0	99 0
V	30 3	34 5	29 0	77 1	54 7	63 0

Table V A *Magnesium [Mg^{2+} (mmol/kg d wt)] content of rabbit placenta slices at different periods of gestation incubated 120 min at 0–1 C and 60 min at 38 C in different oxygenated suspending media*

	0–1 C			38 C		
eriod of gestation	Ringer Tris	Plasma	Plasma + 10 mM K^+	Ringer Tris	Plasma	Plasma + 10 mM K^+
II	40 5±1 2 (45)	36 6±1 1 (44)	35 7±2 2 (8)	34 7±1 2 (26)	31 4± 9 (27)	37 4±2 4 (8)
IV	36 7± 8 (18)	32 2± 6 (25)	31 1±1 4 (8)	30 9± 7 (18)	28 7±.5 (25)	34 9±1 8 (8)
V	34 8±1 6 (15)	34 5± 9 (18)	32 4±2 7 (8)	33 0±1 4 (12)	29 2± 6 (18)	30 4±3 6 (8)

Mean±SEM (n of observations) For further details see the text

ncubated in the presence of plasma with added 10 nM K^+ (15 mM final) does Na^+ intracellular con entration decrease to about 90 mM in the period II nd to about 100 mM in the period IV while it is still igh in the slices of the period V

An actual recovery is therefore present only in the ices of the periods II and IV whereas it is absent in ie beyond term placentae It must be noted that ome of the $[Na^+]_i$ calculated in Table IV exceed the $Na^+]_o$ because of experimental error The lculated intracellular concentration of K^+ behaves a way similar to Na^+ The concentration in fact higher in the K supplemented plasma and the up ke at 38 C is greater in the younger placentae

In Table V the results of experiments are reported hich concern the net movement of Mg^{2+} and $^{2+}$ The content of Mg^{2+} does not seem to show nificant variation between the various conditions ted The amount of this bivalent cation is constant a value of about 30-40 mmol/kg d wt with small illation of no statistical significance and unrelated he design of the experiment

n contrast Ca^{2+} behaves quite differently from a^+ At 0–1 C in fact Ca^{2+} enters the tissue and reases significantly in comparison with fresh tissue When the slices are transferred to 38 C a net vement of Ca^{2+} is evident This happens especial n the slices suspended in the K^+ supplemented ma Ca + content in fact decreases significant the slices of period II and IV to values which are ly similar to those of the fresh tissue (2) The effi cy of the expulsion decreases from 60–90 per to 30 per cent in the beyond term placentae In bation in Ringer Tris and plasma alone the + in the tissue at 38 C increases to values higher at 0–1 C

n the basis of the results shown up to now we ed for a possible correlation between the bolic condition of placenta slices incubated at 38 C and both the age of the tissue and the incuba tion medium To this purpose we measured the O_2 consumption of the slices from placentae at different periods of gestation incubated at 38 C after cold preincubation in the three different media Under certain circumstances respiration can be considered as good parameter for evaluating cell energy metabolism

The results are reported in the last Table (VI) The rate of oxygen uptake is primarily dependent on the age of the tissue as had been previously shown on different placental systems (5 7) but it is also strongly related to the nature and composition of the incubating medium Respiration in fact decreases significantly by 40–60 per cent in the period IV and V irrespective of the suspension medium On the other hand O_2 consumption increases by 50 and 70 per cent in plasma and K^+ supplemented plasma respectively The increase is less pronounced in the placentae of period V (about 5 per cent) The addition of ouabain inhibits O_2 uptake uniformly by 15 per cent

DISCUSSION

Water movement at 38°C The results presented in the previous section show clearly that placenta cells are able to extrude under the appropriate metabolic conditions a substantial amount of water taken up during the period of incubation at 0–1 C The decrease of the total tissue water is rather small (14–20 per cent) but is accompanied by a more substantial shrinkage of the intracellular compartment This compartment in fact is reduced in size by about 30-60 per cent Although the expulsion of water from placental tissue is dependent on the metabolic state of the cells (it takes place at 38 C) it does not seem to be related to the rate of oxygen consumption and the age of the tissue The expulsion oc

Table IV A *Sodium [Na+,(mM)] intracellular concentration of rabbit placenta slices at different periods of gestation incubated at 0–1 C and 38 C in different suspending media*

Period of gestation	0–1 C			38 C		
	Ringer Tris	Plasma	Plasma + 10mMK+	Ringer Tris	Plasma	Plasma + 10mMK+
II	136 8	171 1	144 5	183 3	154 4	89 9
IV	166 2	160 5	137 3	199 2	154 9	111 5
V	141 6	147 2	145 9	175 5	197 8	162 4

creases to about 40 per cent in the slices of the period II and IV while it is still low (16 5 per cent) in those of period V As far as K+ is concerned the recovery is more pronounced and it also occurs in inverse relation to the age of placenta

These results show that placenta behaves quite differently from other tissues The extensive studies of van Rossum (4 8) indicate that slices from rat liver or from some neoplastic tissues are able to regain in the Na^+ K^+ and Ca^{2+} gradients when they are incubated at 38 C under suitable metabolic condition even when suspended in artificial saline solution

Preliminary experiments which showed that placenta slices incubated at 38 C in Ringer Tris but without the previous incubation at 0–1 C fail to regain ion gradients (results not shown) suggest that the cold incubation does not irreversibly spoil the tissue

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Table IV B *Potassium [K+,(mM)] intracellular concentration of rabbit placenta slices at different periods of gestation incubated at 0–1 °C and 38 C in different suspending media*

Period of gestation	0–1 C			38 C		
	Ringer Tris	Plasma	Plasma + 10mMK+	Ringer Tris	Plasma	Plasma + 10mMK
II	40 9	52 9	46 9	100 7	109 2	179 8
IV	33 0	30 5	39 3	87 3	59 0	99 0
V	30 3	34 5	29 0	77 1	54 7	63 0

We have previously shown that placental ces incubated under metabolically unfavorable con ons (0 – 1 C) equilibrate their ion content with the medium regardless of the period of pregnan In contrast the recovery at 38 C appears to be trongly dependent on the degree of maturity or of the tissue The period II placentae are le to recover almost completely their Na^+ and K^+ nts with an efficiency of about 65 per cent (see II) The efficiency declines to about 50 per cent t term (period IV) whereas it further decreases in lacentae brought beyond term In the latter case ite the decrease in the Na^+ and the increase in he K^+ content of the slices (Table III) the alculated intracellular concentration shows that Na^+ movement is only apparent while that of K^+ is xigous (Table IV) In beyond term placentae the ecrease of tissue Na^+ is than not linked to active passive transfer dependent on water xtrusion The relation between the active movement f ions and tissue metabolic state is proved by the ata concerning the respiration of placental slices in ibated in various media at different periods of station It is apparent that the higher the rate of O_2 nsumption the more efficient the ion translocation acental slice O_2 uptake is in turn dependent on th tissue age and the incubation medium At 38 C agnesium does not show significant changes fur r proving that this ion is one of the most stable in cell it is probably mostly bound to intracellular uctures as in other systems

The behaviour of Ca^{2+} is rather different It in during the cold incubation and is actively ex ded under metabolically favorable conditions The ciency of the extrusion is high (60 – 90 per cent) in period II and IV whereas it declines to 30 per cent the beyond term placentae There is an apparent repancy between the data concerning Ca^{2+} vement in this study compared with those our vious work (3) We increased the concentration of + in the medium in these experiments to a more siological level (5 mM) A higher Ca + content in external medium could increase cell membrane ility and affect its permeability to other ion ies (Na^+ and K^+)

We wish to emphasize the influence of the com ition of the incubating medium on placenta tissue ctions We have seen that plasma and the further ition of 10 mM K^+ to plasma improves both iration and ion translocation in placentae In par lar the K^+ supplemented plasma is the only medium in which a real gain of ion gradients (Na^+ K^+) takes place and it is the only condition in which net extrusion of Ca + is evident These observations are of general interest in improving placental perfor mances during *in vitro* studies

CONCLUSION

The results obtained in the present work lead us to the following conclusions Rabbit placenta slices in cubated under metabolically favorable conditions after a period of preincubation at 0 – 1 C are able to bring about the net extrusion of Na^+ and Ca^{2+} and the uptake of K^+ The active movement of ions i strictly dependent on the incubation conditions the presence of high [K^+] being essential Further Na^+ and Ca^{2+} extrusion and K^+ uptake take place more efficiently in younger placentae decreasing toward the end of pregnancy and disappearing in the tissue pharmacologically brought beyond physiological term The net ion movement is finally tightly coupl ed to the cell energy supply We have demonstrated that a direct relationship exists between the O_2 consumption rate and ion movement Tissue oxygen uptake is in turn influenced by the incubation condi tions and tissue age Finally placental slices in cubated in oxygenated medium at 38 C extrude the excess water taken up during its stay at 0 – 1 C by metabolism-dependent mechanisms The water extru sion unlike the recovery of ion gradients takes place with equal efficiency regardless of the nature of in cubation medium and of the age of the tissue

Further studies are in progress to better define the source of the energy necessary for the maintenance of ion gradients and the biophysical characteristics of the process

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A LONGTERM ISOTOPE RENOGRAPHY FOLLOW UP OF PATIENTS FOLLOWING PREGNANCY COMPLICATED BY PRE ECLAMPSIA AND HYPERTENSION

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Abstract 61 patients were studied with the renography and urography during puerperium ten years ago and now again The technique and analyses were identical The results showed that some of these parameters (SV K and T 1/2) were either decreased or prolonged more than ten per cent during this period in nearly all cases However these changes occurred in both the normal and complicated groups without any correlation with the original diagnosis from the first study Hypertension has developed in 10 per cent of the toxemic group

Whether pre eclampsia or hypertension during ıregnancy causes permanent changes in the maternal ıdneys has been a problem which has occupied many esear hworkers In most cases the changes have dis ppeared during the first few months after delivery 1 2 9) In Friedberg s study (5) 15 per cent of tox mic patients had renal lesions after delivery and 50 er cent were reported in Dieckman s study (4) In oth studies follow up was limited to a few months ost partum In this study renographic findings ob- rved ten years ago (6) were compared with the cur nt findings

MATERIAL AND METHODS

ıe present series consisted of previously examined patients 7 patients after uncomplicated pregnancy 78 after tox ıia and 7 after hypertensive pregnancy Table I) who re invited for a control examination The invitation was accepted by 61 mothers Of these mothers 16 had had an un complicated pregnancy 30 mild and 8 severe pre-eclampsia and 7 chronic hypertension as a complication present at the former examination All patients underwent isotope renography and in 25 cases intravenous pyelography was per formed

Analysis of the renogram The comparison of previous post partum renograms with control renograms was made in accordance with the original analysis i e (6) using as parameters the secretion value (= SV) the accumulation peak (= K) and the half time of the excretion phase (= T 1/2) the main interest being directed towards changes in SV of over 10 per cent

The empirical normal range of the parameters was SV = 1 25 the culmination peak = 6 minutes and the half time of the excretion phase = 18 minutes The SV value represents the tubular capacity to receive the tracer the ac cumulation peak reflects the cellular excretion capacity and T 1/2 mainly the renal excretion of the tracer

RESULTS

Mothers without the complication of hypertension in pregnancy (controls) The changes in SV values are shown in Table 2 SV was increased in 31 per cent of the cases when compared with the previous examina tion totally decreased in 60 per cent in 50 per cent on the left side 69 per cent on the right side and bilaterally in 50 per cent Of three patients in whom the SV values had decreased bilaterally more than 10 per cent one had contracted rheumatoid arthritis

able I *The distribution of the material according to the first study*

ıagnosis	The first study	The second study	Between the studies developed a chronic disease	
	Cases	Cases	Cases	DGN
ormal pregnancy	27	16	1	arthritis
ıld pre-eclampsia	48	30	5	hypertension
vere pre-eclampsia	30	8	2	hypertension
ypertension	7	7	7	hypertension
ətal	112	61	15	

Table II *The SV change in the control group the pre eclampsia group and the hypertension group*

	Control			Mild pre-eclampsia			Severe pre-eclampsia			Hypertension		
	Left	Right	Both	Left	Right	Both	Left	Right	Both	Left	Right	Both
Unchanged	3 (19)			3 (10)	6 (20)	2	1 (12)					
Increased	5 (31)	5 (31)	5	8 (27)	5 (17)	3	1 (12)	1 (12)	1	1 (14)		
Decreased	8 (50)	11 (69)	8	19 (63)	19 (63)	17	6 (75)	7 (88)	6	6 (85)	7 (100)	6
Change > 10 per cent	5 (31)	9 (56)	3	10 (33)	13 (43)	6	1 (12)	1 (12)		4 (57)	7 (100)	4
Cases no	16	16		30	30		8	8		7	7	

Both = The simultaneous change in both kidneys
The figures within parenthesis denote number in per cent

The culmination peak (Table 3) had remained un changed in 62 per cent increased in 28 per cent and decreased in only 9 per cent of the control patients

The half time of the excretion phase showed no change in 25 per cent it was shortened in 44 per cent and prolonged in 19 per cent of the cases T 1/2 was impossible to analyse in two renograms (Table 4)

Eight mothers had undergone intravenous pyelo graphy both in 1967 and the present time In one case with a previously normal result hydronephrosis had developed in this patient the above parameters were also decreased The urogram of the rheumatoid pa tient had been abnormal at the first examination

Mild pre-eclampsia The SV value was unchanged bi laterally in 7 per cent of the cases increased in 10 per cent and decreased in 57 per cent There was a de crease in both kidneys in 63 per cent of subjects Five patients had become hypertensive and in all these cases the SV value was decreased on both side

The culmination peak was unchanged bilaterally in 50 per cent of the cases shortened in only one and prolonged in 23 per cent

The half time of the excretion phase was unchang ed bilaterally in 17 per cent both shortened in 17 per cent and prolonged also in 17 per cent of the cases

In the cases which had become hypertensive th 1/2 was also prolonged with a simultaneously creased SV value

In this group intravenous pyelography was don 9 cases of which seven were interpreted as normal one case a picture of chronic pyelitis was found another case of the same kind of changes had alre been observed ten years previously In both cases SV values were decreased by 18 per cent

Severe pre eclampsia The SV value was increa bilaterally in one case decreased in six cases change being over 10 per cent in two cases The mination time was unchanged bilaterally in cases (38 per cent) decreased in three cases cent) and increased unilaterally in two cases (24 cent)

The half time of the excretion phase was uncha ed bilaterally in two cases shortened in two cases prolonged in one case in one case an unilateral sh ening in the T 1/2 was observed Intravenous p lography done in two cases showed no patholog changes irrespective of the fact that the other pat become chronic hypertensive

Chronic hypertension The patients in this group ceived hypotensive medication With the exceptio

Table III *The culmination peak in the control group the pre eclampsia group and the hypertension gr*

	Control			Mild pre-eclampsia			Severe pre eclampsia			Hypertension		
	Left	Right	Both	Left	Right	Both	Left	Right	Both	Left	Right	Bo
Unchanged	10 (62)	10 (62)	7	20 (62)	18 (60)	15	3 (38)	3 (38)	3	2 (29)	3 (43)	2
Fast	4 (25)	5 (31)	3	3 (10)	3 (10)	1	2 (24)	2 (24)				
Indefinable					2 (7)							
Prolonged	2 (13)	1 (7)	1	7 (28)	7 (23)	5	3 (38)	3 (38)	3	5 (71)	4 (57)	4

Both = The simultaneous change in both kidneys
The figures within parenthesis denote number in per cent

Table IV *The half time of the excretion in different groups*

	Control			Mild pre-eclampsia			Severe pre-eclampsia			Hypertension		
	Left	Right	Both	Left	Right	Both	Left	Right	Both	Left	Right	Both
Unchanged	4 (25)	4 (25)	3	8 (27)	7 (23)	5	3 (37)	2 (25)	2	2 (27)	4 (57)	3
Fast	8 (50)	6 (37)	4	7 (23)	6 (20)	5	2 (25)	3 (37)	2	2 (27)		
Indefinable	1 (6)	3 (19)	1	7 (23)	9 (30)	7	2 (25)	2 (25)	2	1 (19)		
Prolonged	3 (19)	3 (19)	1	8 (27)	8 (27)	5	1 (13)	1 (13)	1	2 (27)	3 (43)	1

h = The simultaneous change in both kidneys
Figures within parenthesis denote number in per cent

one patient the renogram on the left kidney showed that the SV value was decreased by more than 10 per in all cases and that this was bilateral in four The SV value of the right kidney was decreased more than 10 per cent in seven of the cases

The culmination time was unchanged in two cases and prolonged in four cases

The half time of the excretion phase was unchang d in three cases bilaterally and prolonged in only one ase

Six patients had undergone repeated intravenous ography In two cases pathological changes had lready been observed in the previous examination in tter examination two more cases with rightsided enal changes were found

DISCUSSION

uring ten years 1963 1964 when the first part of this idy took place renography was in the first stages of velopment Nowadays it has reached a permanent as a screening test of tubular function vertheless the mathematical interpretation of the nogram still remains a problem That is why in this tive study the old empirical quantification veloped in Heidelberg was used being independent each other prevents the possible errors in one value om affecting the others In practice it has become dent that the SV value is the most informative of parameters It is impossible to estimate the exact ect of physiological ageing nevertheless in this dy a ten per cent change in the values occurred ring the 10 years between the examinations 18 per cent (7 cases) of our toxemic patients had veloped chronic hypertension This result is similar the studies previously mentioned A decrease in the values had taken place in 68 per cent (83 kidneys) the total study patients and a greater than ten per cent change in 41 per cent (50 kidneys) 44 per cent of the control group 38 per cent of the mild pre eclampsia group 12 per cent of the severe pre eclampsia group and 78 per cent of the chronic hypertension group The decrease was bilateral in 37 patients (61 per cent) and both bilateral and greater than ten per cent in 13 cases (21 per cent)

The low level of the SV of the right kidney is a phenomenon already observed during pregnancy In this study there was a decrease of more than ten per cent on the left side in 33 per cent (20 cases) and on the right side in 49 per cent (30 cases)

The culmination peak time was also prolonged This prolongation can be explained by the decrease in the capacity or affinity of the tubular cells which is probably related to physiological ageing

The time of the excretion phase reflects the speed of the disappearance of the tracer from the measuring field In renograms performed during the puerperium the dilatation of the renal pelvis and the ureter have the effect of prolonging the T 1/2 which makes the comparison between our series unreliable Omitting chronic hypertension the state of health of the patient during the previous pregnancy did not correlate with the present renal function Nevertheless in only nine cases did any of the measured parameters remained unchanged or improve In epidemiological studies in The United States a clear correlation between previ ous toxemia and secondary hypertensive disease has been shown (8) We must not forget too that a hyper tensive family history and obesity are correlated with the existence of chronic hypertension (3) These latter facts may cause difficulties with interpretation of our results Of the parameters used in this study the SV has been shown to be most informative in practice Also in this comparative study the changes in these parameters have told us about hidden renal lesions or overstrain caused by pregnancy and its complica tions

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PROGESTERONE AND HUMAN CHORIONIC GONADOTROPHIN IN SERUM AND PREGNANDIOL IN URINE IN THREATENED ABORTION

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bstract Progesterone and human chorionic gonadotrohin ICG) in serum and pregnandiol in urine were measured in ł patients admitted to hospital because of threatened abor on Blood samples were taken and urine specimens col ted at regular intervals during admission and after scharge during the rest of the pregnancy A reference nge was worked out for each hormone based on the hor one values obtained from the pregnancies proceeding to m The predictive significance of values within and below reference range was determined for the initial sample d for serial samples An association between hormone els and outcome of pregnancy was observed but it is con ded that both single and serial determinations of proges one and pregnandiol and serial determinations of HCG unsatisfactory for the evaluation of threatened abor n However an initial progesterone value below the erence range and HCG values below 10 000 mIU/ml be en the 8th and 15th week of pregnancy was in every case ays followed by spontaneous abortion A hormonal test fetoplacental origin is recommended for monitoring eatened abortion

man chorionic gonadotrophin (HCG) is produced he syncytiotrophoblast in the placenta (8) For ny years the detection of HCG in urine and serum been used to diagnose and evaluate early preg cy The corpus luteum seems to be the main site progesterone synthesis up to the 9th to 11th week pregnancy thereafter the placenta is the main site production (4) Progesterone is mainly metaboliz n the liver and about 10 – 15 per cent is excreted in urine as pregnandiol (6) The estimation of these nones is a possible way of monitoring early com ated pregnancy The value of progesterone preg diol and HCG in evaluation of the prognosis in atened abortion has previously been investigated with conflicting results (1 2 7 10)

he purpose of the present study was to estimate prognostic value of both single and serial determi ons of these three hormones in patients with atened abortion

MATERIAL AND METHODS

This study comprised 72 pregnant women consecutively ad mitted to a gynecologic department because of vaginal bleeding with or without lower abdominal pain from the 5th to 20th week of pregnancy Eight patients were excluded for various reasons This left 64 patients in the study They have been described in a previous paper (3)

Blood samples for progesterone and HCG determination were taken shortly after admission and daily for the first five days and then twice weekly while in hospital After discharge samples were taken at least once a month until end of pregnancy Progesterone was measured in all pa tients HCG in all but one Twenty four hour urinary preg nandiol excretion was measured in 50 patients The 24-hour urine specimens were collected twice weekly during admis sion and after discharge at least once a month until delivery The results of the hormone determinations did not influence the treatment of the individual patient

Progesterone in serum was extracted with petroleum ether (bp 40 – 60 C) and estimated by radioimmunoassay with an antiserum raised against 11 alpha hydroxyprogesterone coupled with bovine serum albumin Pregnandiol in urine was measured with a modification of the method described by Kirschner & Lipsett (5) HCG radioimmunoassay was carried out by the double antibody technique as described by Odell *et al* (11) The HCG antiserum used cross-react with luteinizing hormone (LH) but the HCG level in serum samples has never been so low that LH cross reaction will influence the assay

RESULTS

Thirty five (55 per cent) of the 64 patients continued pregnancy until at least the 28th week of gestation Twenty nine patients (45 per cent) aborted spontane ously As previously described (3) a 95 per cent reference range was calculated from the hormone values obtained from the pregnancies proceeding to term The reference ranges are indicated on the fig ures All patients who aborted are indicated on the figures single values are marked with a filled circle In cases where more than one determination was

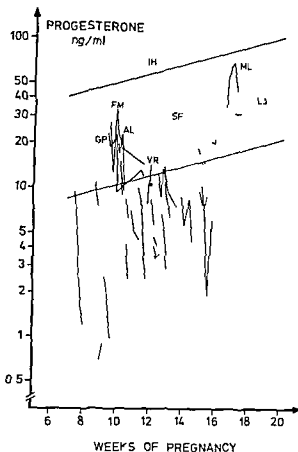


Fig 1 Progesterone in serum in threatened abortion
--- Pregnancies proceeding to delivery
— Pregnancies ending in abortion
Single values from pregnancies ending in abortion The 95 per cent reference range is indicated

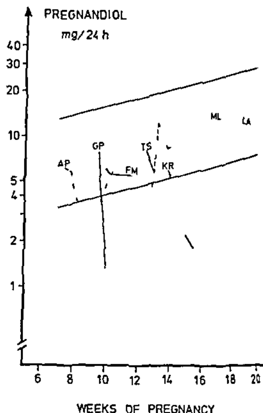
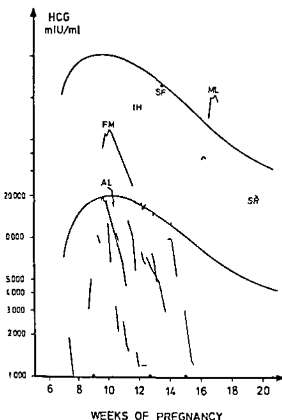


Fig 2 Pregnandiol in urine in threatened abortion
--- Pregnancies proceeding to delivery
— Pregnancies ending in abortion
Single values from pregnancies ending in abortion
The 95 per cent reference range is indicated

made the values are connected with solid lines Values from pregnancies ending in delivery at term are only indicated if any value from the first five days was below the lower limit of the reference range They are connected with broken lines Values are described as low if they fall below the lower limit of the reference range and normal when within the reference range

The results of the progesterone determinations are presented on Fig 1 Only 18 of the 29 patients who aborted had low values at the first blood sample The first value thus erroneously predicted favorable outcome of the pregnancy in 11 patients who later aborted spontaneously After serial determinations progesterone levels were low in 23 of the patients that subsequently aborted Two patients (GP FM) presented *fluctuating values but at the time of abortion values* were normal One patient (VR) showed increasing values from below to within the reference area predicting a favourable outcome At the first blood sample all patients who continued pregnancy values After serial determinations one patient presented decreased values and later one low predicting unfavorable outcome The fol values increased and were later normal again

In 50 patients the pregnandiol excretion in 24 urine specimens were determined Results are ented on Fig 2 At the first determination five o 15 patients who later aborted showed normal v predicting favorable outcome Ten patients had values After analysis of serial specimens one fir patient (GP) had low values after an abrupt decr In three patients (FM TS KR) who showed lo *levels of pregnandiol the values were still norm* the time of abortion Of the 35 patients contin pregnancy only one (LA) had a low value at th urine specimen after serial determinations the *were normal* On the other hand another patient showed a sharp decline to a value far below ence area predicting unfavorable outcome Foll values however were normal



ig 3 HCG in serum in threatened abortion
Pregnancies proceeding to delivery
Pregnancies ending in abortion
Single values from pregnancies ending in abortion
he 95 per cent reference range is indicated

HCG in serum was determined in 63 patients the sults are shown on Fig 3 None of the 35 pregnan proceeding until delivery had low values at the st sample After serial determinations one patient R) showed values falling to levels below the refer ce range At this gestational age falling levels of CG are expected but less than found in this patient e values thus initially predicted unsuccessful out me but the following values increased and were er all normal Concerning the 28 patients who orted 23 showed low values at the first sample ter serial determinations one further patient (AL) d low values Another patient (FM) who eventual aborted presented decreasing levels of HCG but this time of pregnancy decline in the values was ex cted

In Tables I II and III the predictive values for each rmone are calculated based on the first blood sam and first urine specimen and on serial determinations Increasing values and/or a rise of concentration into the reference range was regarded as a positive sign predicting favorable outcome of the pregnancy the contrary a negative sign predicting unsuccessful outcome

DISCUSSION

In previous studies progesterone determinations were found of diverging value in threatened abortion Kunz & Keller (7) found the test of good prognostic value whereas Nygren *et al* (10) found that progesterone rendered an uncertain prediction mainly because of a great deal of overlapping between the two groups of patients

In the present study the progesterone values in the patients who subsequently gave birth showed great individual variations from day to day during the first days of admission and from week to week later in pregnancy (e g LJ Fig 1) Moreover the spread was large These findings are in agreement with Lindberg *et al* (9) who investigated 32 healthy pregnant women serially throughout pregnancy They also found large but non systematic diurnal variations When a decrease occurs in the progesterone level the problem arises whether it is a token of inevitable abortion or just a normal phenomenon This may result in misjudgement of the prognosis and could lead to the evacuation of a normal pregnancy Tulchinsky & Hobel (14) found that the progesterone levels in ten healthy pregnant women did not rise from the 5th to 10th week of pregnancy Values in this period were only slightly above those observed in the luteal phase of the menstrual cycle After the 10th week a significant rise was found Consequently steady levels of progesterone in early pregnancy are not necessarily pathological

Table I *The predictive values for progesterone in serum*

	First sample		Serial samples	
	Pat s who aborted	Pat s who gave birth	Pat s who aborted	Pat s who gave birth
Low values	18	0	23	1
Normal values	11	35	6	34

Predicti e alue of a positive test in first sample 18/18 × 100% = 100% in serial samples 23/24 × 100% = 96%
Pred cti e value of egat e test in first sample 35/46 × 100% = 76% in serial samples. 34/40 × 100% = 85%

Table II *The predictive values for pregnandiol in urine*

	First sample		Serial samples	
	Pat s who aborted	Pat s who gave birth	Pat s who aborted	Pat s who gave birth
Low values	10	1	11	1
Normal values	5	34	4	34

Predictive value of a positive test in first sample 10/11 × 100% = 91% in serial samples 11/12×100% = 92%
Predictive valu of a negative test in first sample 34/39 × 100% = 87% in serial samples 34/38×100% = 89%

At the first progesterone determination in this study all patients whose pregnancies were successful had values within the reference range i e no false positive values were found At first glance the predictive values for progesterone (Table I) especially that for a positive test seem satisfactory However 11 of the 29 patients with unsuccessful outcome of pregnancy had values within the reference range at the first blood sample In other words a considerable overlap was found between the two groups Because of this we find both single and serial determinations of progesterone of limited value in the evaluation of the prognosis in threatened abortion On the other hand the results also show that an initial progesterone value below the reference range in every case is followed by spontaneous abortion

Acevedo *et al* (1) found pregnandiol of prognostic value in threatened abortion Brown *et al* (2) also concluded that the analysis was of value They found that the 50th percentile did not exceed the upper limit of the pregnandiol levels of the luteal phase of the menstrual cycle before the 13th week of pregnancy and the 10th percentile not before the 18th week The pregnandiol values in the present study show the same characteristics in the successful pregnancies as did the progesterone values Great individual variations from day to day and week to week (e g AP Fig 2) a large spread and in early pregnancy normal values not higher than values normally found in the luteal phase of menstrual cycle There was overlap between the successful and unsuccessful pregnancies A 24-hour urine specimen demands careful collection The determination is delayed by the 24 hours occupied by the collection and pregnandiol only reflects a fraction of the progesterone produced For these reasons we cannot recommend pregnandiol determinations for monitoring threatened abortion With an assay for progesterone available we find the tion of pregnandiol obsolete

Nygren *et al* (10) found that a single determin of HCG in serum gave a very good assessment of prognosis in threatened abortion during the first trimester Kunz & Keller (7) also found the analysis of value but recommended its use in association other hormonal parameters Using a specific receptorassay for HCG Rosal *et al* (12) were abl predict spontaneous abortion as early as eight to te days after conception

In early pregnancy there is a very rapid increase the HCG values reaching peak levels between to 12th weeks After this an abrupt fall is seen to minimum values between the 20th to 24th weeks Individual variation is high and the range is large Decreasing values are normal after the 10th week of gestation The gestational age must be known accurately if changing HCG values are to be i correctly Otherwise decreasing HCG values might suggest that the pregnancy is capable of and result in the evacuation of an otherwise pregnancy (e g SR Fig 3) We consider serial H determinations unsuitable for monitoring abortion in spite of its potentially good value (Table III)

All patients continuing pregnancy until deli had HCG values within the reference range at the blood sample The predictive value of the first is very good (Table III) Eighteen patients aborted had values below 10 000 mIU/ml after first sample None of the patients with successful come showed such low values at any time bet 8th and 15th week of pregnancy Thus it reasonable to conclude that HCG values lower 10 000 mIU/ml between the 8th and 15th wee gestation predict spontaneous abortion

Table III *The predictive values for HCG in se*

	First sample		Serial samples	
	Pat s who aborted	Pat s who gave birth	Pat s who aborted	Pat s who gave b
Low values	23	0	24	1
Normal values	5	35	4	34

Predictive value of a positive test in first sample 23/23 × 100% in serial samples 24/25×100% = 96%
Predictive value of a negative test in first sample 35/40 × 100 88% in serial samples 34/38×100% = 89%

In the healthy pregnant woman HCG is only pro- uced in the trophoblast in the placenta From the udy of Scommegna *et al* (13) it is likely that the ex lusive precursor of progesterone synthesis is mater al cholesterol The site of the progesterone synthesis either the corpus luteum or the placenta about 15 er cent is excreted in the urine as pregnandiol All ree hormones reflect only placental or maternal lacental function and tell nothing of fetal function is possible with fetal death but with a still function ig placenta to find normal values of all three hor ones Hormones used for monitoring early compli ated pregnancy should be of fetoplacental origin

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THE DIAGNOSTIC VALUE OF ULTRASONOGRAPHY IN 342 SUSPECTED C OF ECTOPIC PREGNANCY

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lbstract The value of ultrasonography as a diagnostic or :reening tool is studied in 342 cases of potential ectopic regnancy Ultrasonography was used as a diagnostic :chnique when the echopattern was clear enough to pose a iagnosis of ectopic or non-ectopic pregnancy including *tra* uterine pregnancy abortion or other pelvic abnor alities Diagnosis was possible in 77 per cent of the ex nined patients with 95 per cent correct diagnosis 2 per nt false positives and 3 per cent false negatives For trasonography simply as a screening technique whatever e echopattern might be i e in all cases 78 per cent were lected correctly with 20 per cent false positives and 2 per *nt false negatives*

The high quality of the ultrasonic data combined with e relative absence of the disadvantages of roentgen rays d invasive techniques makes ultrasonography the first amination of choise in cases of clinical suspicion of ec pic pregnancy

.cept in cases of Fallopian tube rupture with accom nying internal hemorrhage the diagnosis of ectopic ·gnancy (EP) is difficult When the signs and nptoms of early pregnancy which are not always dent are combined with slight vaginal bleeding derate pelvic pain and palpation of a small para rine mass EP must be considered among the pos 'e diagnoses These symptoms which are not neces ly caused by an EP are quite common They are often seen in cases of abortion associated with the de velopment of a corpus luteal cyst When the symptoms are very characteristic of an EP recourse to complementary examinations is unnecessary The clinical diagnosis is immediately followed by surgical treatment

However the majority of cases are those in which signs of EP are least evident and the diagnosis of EP is just one of many Here complementary examina tions are necessary Among these laparoscopy is con sidered the most useful because it helps avoid un necessary emergency surgery No surgical exploration is completely devoid of risks and laparoscopy is no exception And even if the risk involved is minimal any laparoscopy requires some hospitalization Also laparoscopy cannot be used in every instance because of its inherent contra indications (e g previous abdominal or pelvic surgery)

A technique which could be used instead of lapa roscopy or which could at least select indications for the use of laparoscopy would be greatly appreciated for its help in resolving the problem posed when EP figures in the differential diagnosis This technique must meet certain criteria It must be harmless to the mother and embryo it must be practicable at any mo-

ble I *Annual percentages of ultrasonography indicated for suspected ectopic pregnancy per number of ients examined and per number of examinations respectively*

ır	Total no of patients	No of sus pected EP	per cent	Total no of examinations	No of sus pected EP	per cent
6–68	445	0	0	810	0	0
9	618	5	0 81	1 377	5	0 36
0	1 170	12	1 03	2 400	12	0 50
1	1 466	17	1 16	2 918	19	0 65
2	1 973	32	1 62	3 763	35	0 93
3	2 325	65	2 80	4 500	71	1 57
4	2 600	101	3 88	4 824	113	2 34
5	3 018	69	2.29	5 209	79	1.52
6	3 268	70	2 14	5 228	79	1 51
al	16 883	371	2 19	31 029	412	1 33

ly A-mode scanner available

Table II *Annual results with ultrasonic diagnosis (U D) controlled with invasive techniques (I T), clinical follow up (C F)*

Year	No of suspected EP	I EP			II EP Possible			III EP Excluded			I T Diagnosis	
		U D correct (I T +)	U D false + (I T −)	U D false + (C F)	U D correct (I T +)	U D false + (I T −)	U D false + (C F)	U D correct (I T −)	U D correct (C F)	U D false − (I T +)	(EP+)	(EP−)
1969	5	1	–	–	–	–	–	2	1	1	2	2
1970	9	–	–	–	1	1	1	1	2	3	4	2
1971	14	1	–	–	1	3	1	5	2	1	3	8
1972	30	1	2	–	4	10	–	2	11	–	5	14
1973	58	3	1	–	1	8	3	4	38	–	4	13
1974	93	7	2	–	–	8	5	11	59	1	8	21
1975	67	1	1	–	6	9	6	5	39	–	7	15
1976	66	6	–	–	2	3	4	13	36	2	10	16
Total	342	20	6	–	15	42	20	43	188	8	43	91
Per cent	100	5 9	1 8		4 4	18 1		67 5		2 3	12 6	26 6

ment it should not necessitate anesthesia hospitalization or cause undue discomfort to the patient its diagnostic value must be demonstrated The data obtained by ultrasonography are being appreciated more and more in all medical areas as echographic techniques are improved (e g grey tones) and the practitioners become increasingly skilled at interpreting the various abnormalities which can be encountered To us ultrasound seems to fill all the above criteria leaving only the final criteria of its value in diagnosing EP to be established Since ultrasonography was proposed for exploring the pelvis (1 6) attempts to apply this technique to EP diagnosis have given mixed results These will be discussed later in this study

We hope that our experience involving 371 cases using ultrasonography when an EP was clinically assumed will show how these techniques might help to solve a difficult diagnostic problem

MATERIAL AND METHODS

Patients From 1966 till 1976 16 883 patients ed by the Ultrasound Diagnostic Department Obstetrics and Gynecology Clinic University Brugmann necessitating 31 029 ultrasonographi tions Possible EP was the indication for 371 patients (Table I) Twenty nine patient *involved in a follow up were withdrawn from the* studied the 342 remaining cases form the basis study

It should be noted that ultrasound examinations *ried out on 17 other patients for diverse reasons* prior suspicion of EP However a diagnosis of EP w ed in the ultrasound exam or final protocol These be discussed separately

The validity of ultrasonic diagnoses was vasive techniques (IT) i e laparoscopy and/or in 134 of the 342 cases (39 per cent) or by careful follow up (CF) in the remaining 61 per cent E *cases of EP admitted to the clinic and operated on* prior ultrasound examination have been omitted study

Table III *Ultrasonography as a diagnostic tool (U D) in cases with clear echopattern (i e in 265 out of cases or 77 per cent)*

Year	No of suspected EP	No with clear echo	U D correct No	U D correct Per cent	U D false + No	U D false + Per cent	U D false − No	U D false − Per cent
1969−72	58	36	29	81	2	6	5	14
1973	58	46	45	98	1	2	0	0
1974	93	80	77	96	2	3	1	2
1975	67	46	45	98	1	2	0	0
1976	66	57	55	96	0	0	2	4
Total	342	265	251	95	6	2	8	3

Table IV *Ultrasonography as a selective tool (i e for the selection of EP in 100 per cent of cases)*

Year	No of susp pected EP	EP+ Total No	%	Correct No	%	False+ No	%	EP− Total No	%	Correct No	%	False− No	%	Total Correct No	%	F+ %	F− %
69−72	58	27	46 6	9	33 3	18	66 7	31	53 4	26	83 9	5	16 1	35	60 3	31 0	8 6
1973	58	16	27 6	4	25 0	12	75 0	42	72 4	42	100 0	0	0	46	79 3	20 7	0 2
1974	93	22	23 7	7	31 8	15	68 2	71	76 3	70	98 6	1	1 4	77	82 8	16 1	1 1
1975	67	23	34 3	7	30 4	16	69 6	44	65 7	44	100 0	0	0	51	76 1	23 9	0 0
1976	66	15	22 7	8	53 0	7	47 0	51	77 3	49	96 1	2	3 9	57	86 4	10 6	3 0
Total	34?	103	30 1	35	34 0	68	66 0	239	69 9	231	96 7	8	3 3	266	77 8	19 9	2 3

echniques The principles and techniques of ultrasonic ex mination as discussed in numerous references are now ell known (5 7 15) Examinations were carried out with e following equipment ALOKA (SSD 60 BISTABLE STEM 2,25 MHz) and KRETZ TECHNIK (Combison BISTABLE SYSTEM THEN Combison II GREY CALE 2 MHz) The scans were recorded on Polaroid lms or on 4010 Tektronix hard copier Some figures esented here were obtained in 1977 with the SEARLE sonic (Grey Scale) equipment thus after the above entioned period

hographic criteria The most characteristic echographic ttern of EP is as follows The uterus is slightly enlarged or rmal The thickened endometrium or some blood in the rine cavity reflects strong echoes Close by the uterus a ss can be seen which generates ring shaped echoes This resents the gestational sac Embryo can be displayed pro- led the pregnancy has progressed at least to the stage of 7 8 weeks/LMP (Fig 1-4)

Sometimes a mass is visible behind the uterus in the sterior *fornix When the mass is regularly outlined and* choic it corresponds to accumulation of blood in the uglas pouch when irregular and filled with echoes to a ured tube and blood clot (Fig 5-6)

The above mentioned echogram is protocolled as *EP hly probable* If despite all indications the diagnosis can be made with absolute certainty it is because we feel t only macro- or microscopic examination will verify the stence of an EP

Because this typical echo-pattern is rarely encountered following less typical images must be considered

EP probable when the echogram is composed of a auterine mass with some echoes vaguely arranged in a g echo-pattern next to a well-defined non gravid uterine ity (Fig 7 10)

EP possbile is used for patients with evidence of early gnancy when a mass is found next to the uterus but hout any ring echo-pattern inside (Fig 11 13)

EP excluded a diagnosis of EP can be reasonably ex ded if the gestational sac is visible in the uterus or if the vic echogram is normal even in the face of symptoms of early pregnancy (Fig 14 15) Other diagnoses are given in se cases *for example* evolving pregnancy missed abor 1 complete or incomplete abortion ovarian cyst etc (8)

RESULTS

To simplify the presentation of the data we have divided the cases into 3 major groups formed from conclusions gathered via ultrasonic examinations (Table II)

Group I or *EP* all cases labelled *EP highly probable* and *probable*

Group II or *EP possible* cases where EP was men tioned only as a simple possibility accompanied by either a recommendation of careful surveillance or laparoscopic examination

Group III or *EP excluded* cases where echography showed EP to be highly improbable

These groups were subsequently subdivided as a function of the final diagnosis (correct false positive or negative) and further information is given regar ding the method used to verify the ultrasonic diag nosis 1) Invasive techniques (IT) subdivided into EP positive and EP negative depending on the results obtained 2) clinical follow up (CF) (spontaneous abortion absence of pregnancy or evolutive pregnan cy)

We find that of 26 ultrasonic diagnoses of *EP* 20 were exact and 6 false positives In 239 ultrasonic di agnoses of *EP excluded* 231 were exact and 8 false negatives Among 77 cases diagnosed *EP possible* by ultrasound 15 were actually found to be EPs

In 17 out of the 8 646 patients examined ultra sonically during the last 3 years of the above men tioned period *for reasons other than suspicion of* EP a diagnosis of EP was posed either by ultra sounds or later by other means In these cases an ultrasonic diagnosis of EP was made in 14 4 correct 10 were false positive and the remaining 3 were false negative

Ultrasonography s utility in cases suspected of be ing EP can be considered in the following lights



Fig 1 6 weeks gestational sac located in ectopic position visible in the Douglas pouch (Combison II)
B bladder C balloon of Foley catheter
S gestational sac U uterus



Fig 3 Ectopic pregnancy 9 week-old embryo (Combison II)
E embryo S gestational sac

A *Ultrasonography as a diagnostic procedure* (Table III) A sufficiently precise echo pattern enables an unequivocal diagnosis This entails a greatly reduced risk of error Ultrasonography may be regarded as a means of diagnosis since a diagnosis considered as certain was made in 285 out of 342 cases (77 5 per cent) (groups I and III) The diagnosis was correct in 251 out of these 265 cases (94 7 per cent) while 6 were false positives (2 3 per cent) and 8 were false nega (3 0 per cent)

Echo patterns showed pelvic anomalies but sufficiently characteristic of EP (group II) in of 342 cases (22 5 per cent) These anomalie found to be an EP in 15 of the 77 cases (19 cent)

B *Ultrasonography as a method of selec pregnancy risk* (Table IV) Bearing in mind cases referred for ultrasonography were selected on the basis of the history and phys



Fig 2 12 weeks gestational sac and fetus above the uterus (Combison I)
E embryo S gestational sac U uterus

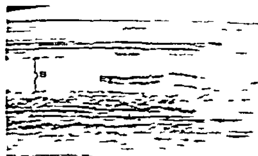


Fig 4 Embryo s body movement displayed by same case as Fig 3 (Combison II)
A maternal abdominal wall E embryo s echo
S gestational sac diameter



ig 5 Ectopic pregnancy enlarged right tube containing ing pattern echoes fluid filled Douglas pouch (Combison I)
B bladder F fluid S gestational sac T tube
U uterus

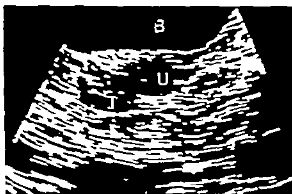


Fig 7 Ectopic pregnancy 5 weeks Enlarged right tube containing irregular ring pattern echoes (SSD 60)
B bladder U uterus T tube

mination one would expect subsequent ultrasonic xamination to confirm or deny the risk of EP In the ormer instance follow up would entail laparoscopy r laparotomy In the latter the patient would be re sured and sent home Seen in this way ultrasounds onfirmed the clinical risk of EP in only 103 of the 12 patients examined or 30 1 per cent (Groups I and) indeed 31 cases were EP i e 34 per cent of the ultrasound risk group When ultrasonography allowed us to estimate as unlikely or nil the risk of EP in 239 of 342 cases or 69 9 per cent (Group III) the risk was incorrectly eliminated in 8 patients i e 3 35 per cent of the ultrasound free-of risk group

Whether ultrasounds were used for diagnosis or solely for screening suspected EPs the number of false positives greatly exceeded the number of false negatives (19 9 per cent versus 3 per cent) Here the cases from the group *EP possible* were placed with those classed as certain diagnoses The discrepancies between false positives and negatives are explained by the prudence exercised by the ultrasonographer the

6 Ectopic pregnancy 4 selected scans showing enlarged nt tube 5 weeks gestational sac uterine cavity io-Sonic)
A transverse and B C D longitudinal scans
uterine cavity S gestational sac U uterus
right tube



Fig 8 Ectopic pregnancy 6 weeks Enlarged left tube and gestational ring (arrow) (Combison I Hard Copy)



Fig 9 Ectopic pregnancy 7 weeks Gestational sac and embryo located in the interstitial portion of the right tube (Combison I)
E embryo S gestational sac U uterus

consequences of a diagnostic error leading to lack of treatment can be disastrous

The chronologic presentation of data beginning in 1969 is designed to evaluate the evolution of these results (Table III and IV) Data from the years 1969 – 72 have been grouped together in view of the minimal number of ultrasonic examinations that were performed for EP in that period One sees that the rate of correct results steadily increases with a corresponding decrease in false positives and negatives among the doubtful cases This evolution can be explained by the experience gained with ultrasonography while the inconsistency in the year to year



Fig 10 Ectopic pregnancy 5 weeks Compare the echoic pattern of the uterus (U) and the anechoic pattern of the gravid left tube (Combison II)



Fig 11 Non typical echo-pattern of ectopic pregnanc irregular outlined mass right to the uterus (U) (Combis Hard Copy)

improvement is due to the rapid turn-over of st the Department

DISCUSSION AND CONCLUSION

Many papers deal with ultrasound and EP only present results (2 3 4, 9 11 12 13 14 16) and been included in Table V

Most of the others (in 9 10 14 16) report case ly When studies are based on a small numb cases the level of correct diagnoses can conce exceed 90 per cent It seems to us that selectio these cases is radically different and for this r we feel that comparison of data would not be ful They are given only as examples



Fig 12 Non typical echo-pattern of left ectopic pr (Pho-Sonic)
A longitudinal scan B transverse scan U ute

Table V *Results literature data on results with ultrasonic diagnosis (U D) for suspected EP*

Year	Authors	No of suspected EP	U D Correct EP No	EP %	Others No	Total No	Total %
1969	Kobayashi *et al* (4)	39	16	41	13	29	74
1970	Zacutti *et al* (16)	30	22	73	6	28	93
1971	Jouppila (3)	17	3	18	8	11	65
1972	Suk *et al* (12)	10	7	70	–	7	70
1972	Varma (13)	20	5	25	13	18	90
1975	Schlensker (11)	47	10	21	34	44	94
1976	Walch *et al* (14)	52	11	21	33	44	85
1976	Levi (9)	87	14	16	46	60	69
1976–77	Hassid (2)	65	13	20	46	59	91
Present study		342	35	10	231	266	78

Table V continuation

J D Incorrect alse+ No	False– No	Total %	Verified EP No	Per cent
5	5	26	21	54
2	–	7	22	73
–	6	35	9	70
3	–	30	7	70
1	1	10	6	30
1	2	6	12	26
6	2	15	13	25
4	3	32	17	20
2	4	9	17	26
8	8	22	43	13

We are convinced that an improvement in the sults can be achieved by reducing the number of lse positives and negatives We believe this is possi e

by repeating ultrasonic examinations more often en possible

by requiring the ultrasonographer to perform a stematic vaginal examination

3 by making sure that the ultrasonic examination is performed under optimum conditions i e bladder properly filled use of high-quality ultrasonic equipment manned by an experienced ultra sonographer

It must also be mentioned that the diagnostic value of invasive techniques which are not repeatable in the event of failure depends on similar factors i e anatomical condition the quality of materials and the capacity of the examiner

13 Non typical echo-pattern of left ectopic pregnancy and tube lies in the Douglas pouch (arrow) (Pho-Sonic)



Fig 14 Intra uterine pregnancy 5 weeks (Pho-Sonic) Arrows shows the gestational sac



Fig 15 Normal pelvis 6 weeks amenorrhea slight bleeding and right mass palpated (O = right ovary *U* = uterus) (Pho-Sonic)

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URINARY ESTROGEN EXCRETION AND CONCENTRATION OF SERUM HUMAN PLACENTAL LACTOGEN IN PREGNANCIES FOLLOWING LEGALLY INDUCED ABORTION

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Abstract Feto-placental function was assessed by 24-hour excretion of estrogens in urine and by the concentration of Human Placental Lactogen (hPL) in serum in pregnant women whose previous pregnancy was terminated by legally induced abortion The mean 24-hour excretion of estrogens in urine and the mean concentration of hPL in serum were no lower in this group than in women without previous induced abortion Neither was the frequency of a low 24-hour excretion of estrogens in urine or low concentration of hPL in serum (values less than mean 1 96 s) found to be increased

This study could not demonstrate an increased frequency of dysfunction of the feto-placental unit during the last part of pregnancy in women with previous legally induced abortion These findings indicate that legal abortion does not seem to increase the frequency of retarded intrauterine growth in a subsequent pregnancy

Legal abortion generally includes instrumental dilatation of cervix uteri followed by an evacuation of the uterine cavity either by the suction method or by curettage Both procedures may cause lesions of the uterus either as lesions of the cervix or lesions leading to defects in the uterine cavity or synechia as demonstrated by Krajl and Lavric (13) and von Seewald *et al* (18) It remains to be clarified if such lesions increase *the risk* of prematurity in a subsequent pregnancy either because of cervical insufficiency or because of compromised placental function leading to retarded intrauterine growth Harlap and Davies (10) found an increased risk of prematurity in women who had previously had an induced abortion However this was not confirmed by Daling and Emanuel (6) Obel (16) nor Roth and Aoyama (19)

This study tries to clarify whether feto-placental function is seen more frequently in women whose previous pregnancy had been terminated by a legally induced abortion by assessing urinary excretion of estrogens and the concentration of serum human placental lactogen (hPL) during the last part of pregnan

MATERIAL AND METHODS

The study included 576 women whose previous pregnancy had been terminated by a legally induced abortion registered during the period 1st April 1974 to 31st December 1975 for delivery at the Rigshospitalet and Frederiksberg Hospital in Copenhagen These women group 1 were compared with different control groups selected from among the other women registered for delivery during the same period

The following control groups were described

Group 2 All women whose previous pregnancy had ended in a spontaneous abortion or stillbirth (1 009)

Group 3 Women whose previous pregnancy had ended in delivery of a live child (539)

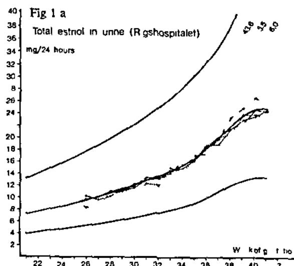
Group 4 Women with no previous pregnancies (337)

Groups 3 and 4 were matched to group 1 using the matched pair technique Age (5 year groups) socio-economic status and parity were used as matching criteria Women in group 1 with only one previous pregnancy terminated by a legal abortion were matched with women of group 3 with parity 1 in addition to women in group 4 As group 3 is smaller than group 1 suitable matches for all women in group 1 were not obtainable from group 3

An analysis of the population as well as the matching procedure adopted have previously been described Obel (16 17)

We aimed at measuring the excretion of estriol in urine *and the concentration of hPL in serum at least twice during* the pregnancy It was not possible to measure the hormones mentioned twice in all patients as some moved districts and some did not want to take part in the study The study also included all hormonal values undertaken for an obstetrical reason The matching procedure was rather protracted and not until afterwards did we learn which women were included in groups 3 and 4 Owing to this delay the number of measurements in group 3 and 4 is smaller than in groups 1 and 2

The two hospitals adopted different methods for measuring the excretion of estriol in urine At Rigshospitalet the 24-hour excretion of estriol in urine was tested according to the method described by Frandsen (7) At Frederiksberg Hospital they adopted the method described by Brown (5) to measure the total amount of estrogen in urine (In the last part of pregnancy estriol amounts to 95 per cent of the total estrogens measured Adlercreutz and Luukainen (1))



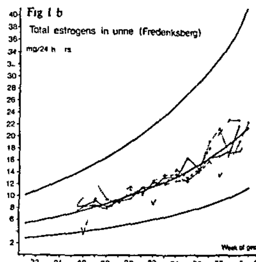


Fig 1 a b Excretion of estriol (in Frederiksberg Hospital total estrogen excretion) in urine during the last part of pregnancy in women grouped according to the outcome of the previous pregnancy The figure shows the mean values in the following groups
— Group 1 Women whose last pregnancy was terminated by legally induced abortion
-- Group 2 Women whose last pregnancy ended *neous abortion or stillbirth*
Group 3 Women whose last pregnancy ended of a live child
Group 4 Women with no previous pregnancies

The concentration of hPL in serum was also measured by different methods in the two hospitals Rigshospitalet adopted the method described by Gæde and Nørgård Pedersen (9) whereas Frederiksberg Hospital used the method of Lebech and Borggård (14)

Because of the different methods used at the two hospitals the results from each hospital have been analysed separately

For statistical analysis we presumed that the excretion of estriol in urine as well as the concentration of hPL in serum had a logarithmic normal distribution in each week This assumption was confirmed by histograms of the values measured for each gestational week as well as fractile diagrams of the logarithm of the observations

Mean hormonal values in women delivering only one child weighing more than 2 500 grams were in each gestational week compared with equivalent values in women delivering only one child over 2 500 grams without any pregnancy complications This comparison revealed no systematic differences In order to define the reference area with as great an accuracy as possible the calculations were then based on the considerably larger group of women who had delivered only one child weighing more than 2 500 grams

The reference area was determined by calculating the mean and the variance of the logarithm of the observations for each pregnancy week from week 21-41 The curve obtained has a linear trend from week 21 to 33 A smoothed curve of mean values was then determined by means of a combination of linear regression up to week 33 and then in the last part of pregnancy by moving average The reference area is in each pregnancy week based upon 95 per cent confidence intervals

RESULTS

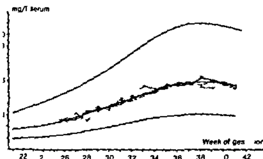
563 women in group 1 delivered and 13 spontaneously In group 2 967 delivered 523 3 and 328 in group 4 whereas there were 42 spontaneous abortions respectively

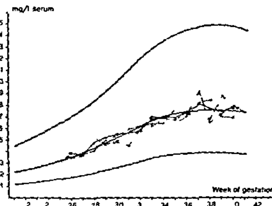
In group 1 91 9 per cent in group 2 90 8 per 83 8 per cent in group 3 and in group 4 82 8 had urinary estrogen excretion measured at during the pregnancy Serum hPL was estima least once for 89 9 per cent in group 1 89 0 in group 2 82 6 per cent in group 3 and in for 80 9 per cent

When comparing the number of women in th groups with 1 2 3 or more hormone tests we that more measurements had been made in and 2 than in groups 3 or 4 x $p<0\ 001$

Fig 1 indicates the mean 24-hour estriol in urine (at Frederiksberg Hospital estrogen) in each of the groups 1-4 The ref area is also marked in the figure *Fig 2* ha equivalent rates as regards hPL As it appears these figures we did not find any difference values of neither excretion of estrogen nor of hPL tween group 1 and the other groups

Table I includes women in groups 1 2 and 3 only one previous pregnancy as well as wome group 4 It shows the number of women with at one hormone value below the lower limit of reference area a well as the number of women





ig 2 a b Mean concentration of serum human Placental Lactogen during last part of pregnancy in women grouped according to the outcome of the previous pregnancy
- Group 1 Women whose last pregnancy was terminated legally induced abortion

— Group 2 Women whose last pregnancy ended in spontaneous abortion or stillbirth
Group 3 Women whose last pregnancy ended in delivery of a live child
Group 4 Women with no previous pregnancies

l values above this limit during the intervals 30-33 1-37 and 38-41 weeks gestation

The number of women in group 1 with at least one hormone level below the lower limit of the reference a during the 4-week intervals mentioned was not nificantly greater than in groups 2 3 and 4 •0 025 (Fisher s exact test) Within each of the week intervals we then determined whether the mber of hormone tests differed between the oups More measurements of urinary excretion of rogen as well as of serum hPL had been carried out groups 1 and 2 than in groups 3 or 4 but the dif ence was not significant x^2 $p>0\ 05$

Table II shows the number of women with at least hormonal value below the lower limit of the erence area (2 5 percentile) in women whose in ts weighed under and over 2 500 grams respec ly In all 4-week intervals we found a significantly ber incidence of women with low values among se delivering infants with a birth weight below 00 grams than among the women delivering in ts with a higher birth weight x $p<0\ 05$

DISCUSSION

purpose of the present study was to determine if rded fetal growth could be demonstrated in wom whose previous pregnancy was terminated by a ully induced abortion Koller and Eikhom (12) nd evidence of fetal growth limitation in women h a previous legally induced abortion In this oup they found that infants born after 36 weeks tation had a significantly lower birth weight than nts of other women the difference was especially marked after 41 weeks of gestation and the authors took this as a sign of growth limitation in women with a previous induced abortion

Excretion of estrogen in urine Beicher and Brown (3) Bjøro (4) and Frandsen *et al* (8) as well as the concentration of hPL in serum Bellman and Lang (2) Hartog (11) and Lindberg and Nilsson (15) have previously been described as being correlated with fetal growth values often being low in cases of retarded fetal growth This study also showed that excretion of estrogen in urine as well as the concentration of hPL in serum correlated with birth weight so that low values were more frequently demonstrated in women delivering infants with birth weight below 2 500 grams than in women delivering infants with birth weight over 2 500 grams

The analysis of the mean excretion of estriol in urine (at Frederiksberg Hospital total estrogen) and the mean concentration of hPL in serum did not demonstrate an increased frequency of feto-placental dysfunction in those women whose previous pregnancy had been terminated by a legal abortion

Even so it might still be possible for instance if the distribution of the values observed varied between the groups assessed that feto-placental dysfunction might appear more frequently in pregnancies following legal abortion compared with others

In order to investigate this problem we have for 4-week cohorts in the last part of pregnancy estimated how many women within each cohort had values below the lower limit of the reference area (2 5 percentile)

Table I *Women with excretion of estrogen in urine and concentration of human Placental Lactogen in se below the 2 5 percentile during last part of pregnancy The women are grouped according to the the previous pregnancy Group 1 2 and 3 Women with only one previous pregnancy terminated by le induced abortion spontaneous abortion or stillbirth and delivery of a live child respectively Group 4 with no previous pregnancy*

Gestation Week	Group 1 Hormone level			Group 2 Hormone level			Group 3 Hormone level			Group 4 Hormone level		
	All obser vations No	At least one obser vation† No	%	All obser vations No	At least one obser vation† No	%	All obser vations* No	At least one obser vation† No	%	All obser vations* No	At least one obse vation† No	%
Estrogen in urine												
Rigshospitalet												
30-33	143	5	3 4	251	11	4 2	101	2	1 9	73	6	7.5
34-37	153	11	6 7	254	17	6 3	168	7	4 0	136	13	8 9
38-41	116	10	7 9	164	9	5 2	136	9	6 2	119	11	8.5
Frederiksberg Hospital												
30-33	46	1	2 1	46			32	2	5 9	20		
34-37	45	1	2 2	47	1	2 1	67	1	1 5	58	3	4 9
38-41	10			15	3	16 7	20	1	4 8	25	3	10 7
hPL in serum												
Rigshospitalet												
30-33	151			248	9	3 5	74	2	2 6	61	2	3.2
34-37	152	3	1 9	245	12	4 7	175	1	0 6	135	3	2.2
38-41	99	3	2 9	131	11	7 7	120	5	4 0	108	2	1 8
Frederiksberg Hospital												
30-33	45			47	1	2 1	57	3	5 0	47	1	2 1
34-37	48	1	2 0	49	1	2 0	68	2	2 9	68	2	2.9
38-41	11	2	15 3	13			31			24	1	4 0

>mean − 1 96 s
† ≤mean − 1 96 s

Groups 1 3 have been described according to the outcome of the previous pregnancy whereas women in group 4 had no previous pregnancies therefore parity varies between our groups It has been demon strated previously that the number of previous preg nancies was higher in groups 1 and 2 than in group 3 and that the frequency of low birth weight as well as of short gestational age increased with increasing parity and with the number of previous pregnancies Obel (17) Because of the difference mentioned be tween the groups we decided for analysis of the group of women with low hormonal values only to study those with one previous pregnancy and women in group 4

The number of women with at least one low value of a hormone measured will by chance increase with the number of tests performed The correlation between the number of tests and the number of wom en with at least one low value is in this study further accentuated because often a low hormone value but still within the reference area may be followed by ad ditional measurements as the woman in question is looked upon as an obstetrical risk patient

During the intervals 30-33 34 37 and 38-41 gestation the number of hormone est groups 1 and 2 was found to be a little higher bu significantly higher than in groups 3 and 4 Th ference in the number of measurements indicate more women with at least one value below the l limit would be expected to be in groups 1 or 2 r than in groups 3 or 4 But in spite of this we c not demonstrate significantly more women in gr with at least one hormone assay below the lower of the reference area (Fisher s exact test $p>0.0$

CONCLUSION

The present study could not demonstrate an incre frequency of low urinary excretion of estriol Frederiksberg Hospital total estrogen) or tration of serum hPL in women whose previous nancy was terminated by a legal abortion when pared with control This finding does not suppor theory that retarded fetal growth is more fre after induced abortion

able II *The correlation between the excretion in urine as well as the concentration of human Placental Lactoen in serum below the 2 5 percentile during the last part of pregnancy for women with normal and low birth veight infants*

		Rigshospitalet Birth weigth				Frederiksberg Hospital Birth weight			
		≤2 500 g No of women with values <mean 1 96 s		>2 500 g No of women with values <mean 1 96 s		≤2 500 g No of women with values <mean 1 96 s		>2 500 g No of women with values <mean 1 96 s	
	Gestation Weeks								
strogen in urine	30-33	13	13 0%	35	3 3%	1	12 5%	8	3 1%
PL in serum	30-33	8	7 8%	26	2 6%	1	8 3%	6	2 0%
strogen in urine	34-37	21	22 8%	70	5 5%	3	23 0%	16	5 0%
PL in serum	34-37	16	18 2%	27	2 2%	3	20 0%	7	2 0%
strogen in urine	38-41	14	32 6%	53	5 4%	3	42 9%	7	5 7%
PL in serum	38-41	6	16 7%	28	3 3%	1	12 5%	4	3 4%

strogen in urine In Rigshospitalet measured as excret on of estriol in urine per 24 hours. In Frederiksberg Hospital measured as the total es-ogen excretion in urine per 24 hours

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HISTOLOGICAL APPEARANCES OF THE HUMAN PLACENTA OBSERVED BY ELECTRON MICROSCOPY AFTER HYPERTONIC SALINE ABORTION

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bstract Placentae obtained after Hypertonic Saline In ıced Abortion (HSIA) were compared with placentae de ered by hysterotomy between 16 and 20 weeks of preg ıncy When investigated by routine light microscopy the eater part of the placental tissue seemed to be normal anges were confined to a thin subchorionic layer Trans ıssion and scanning electron microscopy revealed serious ımage especially to the syncytium not only in the sub onal zone but also in the transitional and in the decidual ne In vitro experiments demonstrated that a very short posure to hypertonic solution can produce impressive tological changes in placental tissue

e mechanism of initiation of uterine contractions abortion following intra uterine injection of ıertonic saline or other hypertonic solutions has been completely elucidated up to now In the 0 s Csapo formulated his theory (1 5 6) which ısed much controversy According to Csapo hy tonic solutions could damage the placenta and with its endocrine function This would then ılt in progesterone withdrawal and abolition of the ogesterone block

his theory has been challenged in three different ds of investigation In the field of endocrinology a concerning urinary pregnanediol excretion and ma levels of progesterone and other placental mones after instillation of hypertonic saline re ned controversial (7 8 14 15 16 18 20 22 23

he second field of controversy concerns the pros andins The work of Gustavii (11 12) suggests one of the factors involved in the mode of action ıtra uterine hypertonic saline is the release of pro- landins from damaged decidual cells This ever need not be considered as contradictory to theory of progesterone withdrawal but could be plementary to it Walker *et al* (25) observed that addition of hypertonic urea to an intra amniotic abortifacient dose of prostaglandin $F_{2\alpha}$ decreased the plasma progesterone level and reduced the instilla tion abortion time

The third field of controversy concerns the results of microscopic examination of the placenta after hy pertonic saline abortion Several investigators have found lesions of the subchorionic layer of the placen ta (2 4 10 13) the most extensive investigations hav ing been made by Christie *et al* (4) These authors observed characteristic lesions in 14 placentae after intraamniotic injection of hypertonic saline These le sions were confined to a thin subchorionic layer and even in the most severely affected cases 80 per cent of the placenta was apparently undamaged They concluded that it is improbable that an intra amniotic injection of hypertonic saline induces abortion by causing extensive damage to the placenta and there fore removing the progesterone block These con clusions based on investigations with routine light microscopy up to now have hardly been challenged The only published investigation using electron microscopy is to the best of our knowledge a very short and preliminary communication in an article by Wynn (26) and the conclusions are not essentially different from those of Christie destruction of the fetal surface and maintenance of relative ultrastruc tural integrity in the maternal zone

The aim of this study was to investigate placentae obtained by hypertonic saline induced abortion (HSIA) and by hysterotomy at the same gestational age The investigation carried out by means of trans mission and scanning electron microscopy was in tended to determine the changes in the placenta associated with the instillation of hypertonic saline

MATERIAL AND METHODS

The placentae of 17 patients aborted by HSIA were com pared with 14 placentae delivered by hysterotomy between 16 and 20 weeks of pregnancy Immediately after delivery of



Fig 1 Micrograph of a placenta obtained by hysterotomy Some of the villi are studded with red cells (asterisk) whereas red cells can be observed in other villi (arrows) This phenomenon is very characteristic of a p ed by hysterotomy

the placenta tissue blocks were cut from the subchorial intermediate and decidual parts All placentae were studied by light microscopy in the examination by electron microscopy 5 placentae obtained after hysterotomy and 5 obtained after HSIA were included From every placenta three blocks were studied and from each block several grids were examined

The tissue to be examined by light microscopy was placed in Susa fixative and embedded in paraffin Sections 5 to 6 μm in thickness were stained with haematoxylin and eosin Masson trichrome stain or Alcian Blue PAS Reaction Tissue samples for Transmission Electron Microscopy TEM were fixed in a mixture of 2 4 per cent glutaral dehyde in equal volumes of water and phosphate buffer (0 15 M pH 7 4) for 3 to 4 hours Specimens were embed ded in Epon 812 using routine methods Sections were stain ed with lead citrate and uranyl acetate and observed in a Philips EM 300 at 80 KV Fixation of the specimens for scanning Electron Microscopy SEM was as for Transmis sion EM Specimens were submitted to critical point drying (CPD) via amylacetate and CO_2 The were then coated with gold in an electron gun evaporator and observed in a Coates and Welter Cwicscan Nr 100 at 20 KV

One placenta obtained by hysterotomy received special treatment consisting of immersions in different salt concen trations to determine the immediate effects of hypertonic salt solution Tissue blocks from this placenta as follows

a fixed immediately as described above

b placed for ½ hour in Seligman s balanced salt (SBSS)

c placed for ½ hour in a 2½ per cent solution of SBSS

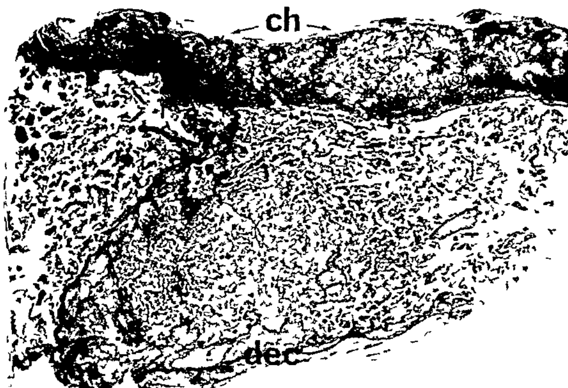
d placed for ½ hour in a 5 per cent solution of SBSS

Subsequently the specimens *b* to *d* were fixed ed for transmission and scanning electron mi experiment was carried out on 5 blocks of placenta were studied afterwards by TEM and SEM

RESULTS

Within their groups (hysterotomy HSIA tal) the placentae showed a very uniform pictu

Light microscopy In the placentae obtained by terotomy the vessels in the placental villi strong overfilling with blood Sometimes were ruptured so that the villi were filled erythrocytes (Fig 1)



2 Transverse section of a placenta obtained after ·tonic saline abortion In the upper region a small part e amnio-chorion (ch) is visible Just below the chorion ic plate (ch) there is a necrotic zone ( ) As is shown the thickness of this necrotic zone is variable In the lower part the decidua basalis (dec) can be observed HE × 20

cross sections of placentae obtained by HSIA a irregular zone of red thrombus is seen directly w the chorion (Fig 2) This thrombotic zone may r up to 20 per cent of the section Histological ırmalities were confined to the thrombotic zone ıe placenta whereas the intermediate and decidual ons had a normal appearance In the damaged the nuclei were pyknotic and there was a variable ee of vacuolization of the cytoplasm We also d infiltration by many polymorphonuclear ocytes as was described by Christie *et al* (4)

tron microscopy

entae obtained by hysterotomy

ransmission E M At this stage of gestation the hoblast still consists of two layers which can be clearly distinguished (Fig 3) The apical zone of yncytiotrophoblast is called the zone of resorp- (9) and contains a great number of microvilli plasmic vacuoles dense bodies and mitochon whereas the region that is occupied mostly by rnae of the RER is called the zone of secretion

Below the syncytium the cytotrophoblast or Langhans layer is found resting on a very well developed basal lamina Between the syncytium and the Langhans layer there is a widening of the intercellular cleft into which microvilli project The cytotrophoblast cells contain cytoplasm which is less electron-dense than the cytoplasm of the syncytial layer they contain well developed Golgi complexes very large mitochondria polyribosomes and many glycogen particles (Fig 3)

B Scanning E M The specimens studied consisted of about 8 – 10 villi and their ramifications (Fig 4) Higher magnifications revealed a good impression of the long slender appearance of the normal microvillous border (Fig 5) The microvilli were often seen to terminate in a small bulbous tip a phenomenon we also noticed in transmission electron microscopy

Placentae obtained by HSIA

a Transmission E M In these placentae it was important to separate the samples into those obtained



Fig 3 Section through the trophoblast of a placenta of 16 weeks gestation obtained by hysterotomy The upper left region shows a part of the syncytium with the microvilli (mv) a protrusion (p) absorption vacuoles (a) mitochondria *(arrows)* cisternae of the RER (c) with ribosomes on their membranes Between the syncytium and the cytotroph*oblast intercellular spaces (s) can be distinguished* trophoblast has an electronlucent cytoplasm in developed Golgi complex (g) and many free pol and glycogen particles can be observed *layers desmosomes (d) are visible* The c on a well-developed basal lamina (bl) × 15 000

from the subchorial region and from the decidual region because after instillation of hypertonic saline solution a concentration gradient exists from the amniotic sac towards the decidual plate In the subchorial zone where the lightmicroscope revealed serious damage also by electron microscopy the greatest signs of disintegration were found The cisternae of the endoplasmic reticulum were greatly enlarged the mitochondria were either swollen or their matrices had become very electron dense microvilli appeared as torn membranes and the nuclei had become pyknotic The first sign of disintegration of a microvillus is a pronounced bulbous swelling even ballooning of its tips This stage is rather rare in the subchorial area where *it is almost always succeeded by a* total disintegration and loss of the microvilli

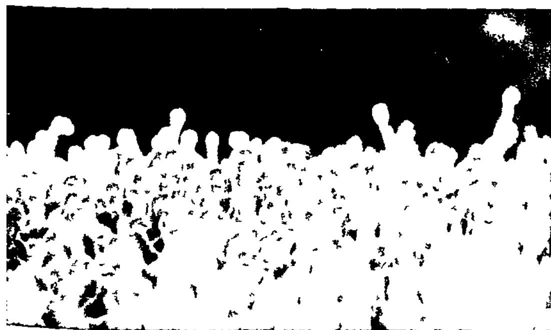
By distension of the endoplasmic reticulum the cell *is becoming rather disrupted* and large portions of the cytoplasm bulge as protuberances from the apical border (Fig 6)

In the decidual zone parts of the sometimes found to appear quite normal inspection showed however that here also nae of the endoplasmic reticulum were more than usual and the mitochondria had electron dense matrix as their cristae Almost all parts of the trophoblastic layer decidual zone however were much more especially the microvillous border (Fig microvilli having become swollen with loss of structure in addition the RER conta distended cisternae

b Scanning E M

Subchorial zone In the scanning el we observed that the slender appearance o had disappeared large swellings protruded villous surface (Fig 7) and large areas had a appearance The microvilli appeared to together to form so called plaques *In add* protuberances the subchorial ballooning effect

Scanning micrograph of a part of the human placenta weeks At this low magnification the ramification of the villi can be seen Between the villi small aggregations of red cells and fibrin are distinguishable (arrow) × 400



Scanning micrograph of a part of a placental villus microvilli have a slender appearance sometimes they have a bulbous tip × 65 000

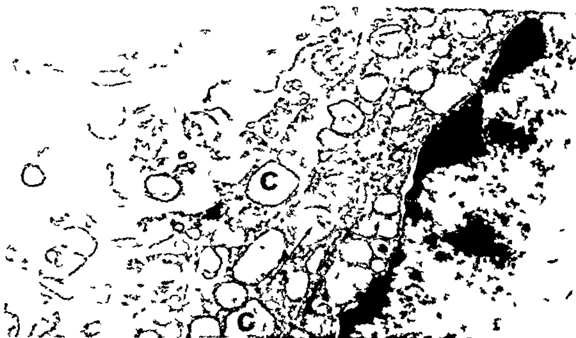


Fig 6 Transmission electron micrograph from the placenta obtained after hypertonic saline abortion The picture shows a part of the syncytium of a villus in the subchorial zone Microvilli have already disappeared and the cytoplasm is disintegrating Vesicles with granular flocular content probably represent cisternae of the en reticulum (c) which are swollen and the nucleu densely clumped chromatin The mitochondria show only slight damage × 20 000

Fig 7 Scanning electron micrograph of the syncytial surface of a placental villus after hypertonic saline abortion Below on the left microvillous structures still can be identified (arrows) although there are already signs of mat... right no microvilli can be identified and the bord... villus shows many of cytoplasmic protrusions (.). × ...



8 Electron micrograph of a villus in the decidual region placenta obtained after saline abortion The difference the electrondense syncytium and the not so dense plasm of the cytotrophoblast cell (cyt) is very clear In layers the mitochondria (arrows) have a normal appearance Note however the swollen cisternae (c) of the in the syncytial layer and the distorted microvilli 2 000

nsitional zone The phenomena observed in the chorial area can also be found in this region The urbances occurred in a milder form however and large ballooning projections which are specific for subchorial zone were not observed in the transitional zone although cytoplasmatic protuberances the matting phenomenon could be found in all of the villi we observed

zone The matting process was the most characteristic phenomenon in this region Although the parts of the villi had a rather normal microvilli border large areas were covered with plaques the other microvilli had pronounced swelling at their tips (Fig 9)

In vitro experiments with hypertonic saline solutions
The tissue changes observed in HSIA might be the result of autolytic processes due to the fact that the fetus had died some time before the placenta becomes available To obtain more information we performed the following in vitro experiment From a normal placenta obtained by hysterotomy small samples were placed for ½ hour in solutions of differing salt concentrations In order to obtain some information about the alterations due to the medium samples were placed for ½ hour in pure isotonic SBSS The specimens were then subjected to TEM and SEM

Results after ½ hour exposure to SBSS The most striking feature in the TEM pictures were the juxta nuclear vacuoles (Fig 10) These vacuoles consisted of a local distension of the nuclear envelope Sometimes vacuoles of this type are described as a common structure in placental anatomy In our opinion these vacuoles are artefacts due to the period of time that the samples were left unfixed in the medium as we did not find them in the specimens of the same placenta which were fixed immediately The cisternae of the endoplasmic reticulum were also a little distended but the microvillous border was intact this was confirmed by scanning microscopy The only change we found with the scanning microscope was a slight swelling of the microvillous tips No signs of matting or cytoplasmic protrusions were found

Results after exposure to hypertonic solutions (resp 2½ and 5 per cent NaCl in SBSS) Exposure to different concentrations of hypertonic saline produced in vitro the same alterations as those described for the placentae obtained after HSIA With TEM disintegration of the syncytial layer and swollen mitochondria in the Langhans layer could be observed (Fig 11) Sometimes the mitochondria and the cytoplasm had become very electron dense probably due to dehydration With SEM the same matting was observed as had been found after HSIA (Fig 12) Large areas of the villi were covered by plaques The tips of the microvilli were swollen and sometimes slight protrusions were present

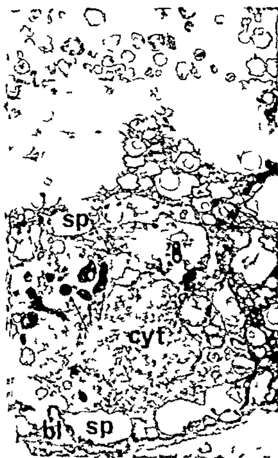
The damage observed after in vitro exposure to hypertonic solutions was more severe when 5 per cent NaCl solutions were used

DISCUSSION

Our investigations of placental histology after HSIA with light microscopy showed damage to the subchorial zone and in about 80 per cent of the placental

Fig 9 Scanning electron micrograph of a placental villus of the decidual zone after hypertonic saline abortion in the 16th week of gestation The left half of the picture shows an area with a rather normal structure although the microvilli have rather swollen tips (arrows) These areas are rare h ever The right part of the photograph shows a charac ic area with the more common matting (asterisk) × 19 000

Fig 10 Part of the trophoblast after treatment for ½ hour in SBSS The juxtanuclear vacuoles (vac) next to the nucleus (n) are very specific for this experiment The microvilli show no changes desmosomes (arrow) and the basal lam are seen In the basal lamina is a dark spot (arr sisting of calcium phosphate deposits × 10 000



11 Transmission electron micrograph of the tropho- after in vitro treatment with 5 per cent NaCl in SBSS mitochrondria (arrows) in both layers are very electro- e the microvilli are bulging and the intercellular spaces are distended The cytplasm of the cytotrophoblast cell shows signs of disintegration × 12 000

ie a normal structure was observed These fin s are in agreement with other investigations (2 4 13)

lowever electron microscopy showed more wide d damage to the placental trophoblast In the chorial zone the changes observed were severe also *in* the intermediate and decidual zones large s of the syncytium were seriously disturbed al igh a gradual decrease in the damage from sub- nal zone to decidual zone could be observed At decidual side occasionally some areas of the villi eared at first sight to be normal It was revealed r further inspection by transmission electron roscopy however that even in these areas there are nges on a cellular level

The Langhans layer seems to be much more resistant towards hypertonic solutions than the syncytial layer

Very soon after instillation of hypertonic saline the fetus dies The changes in the trophoblast however can not be attributed to the death of the fetus Myers and Panigel (17 19) studied the effects of surgical removal of the fetus on the placenta in the Rhesus monkey After 5 days the changes in the placenta observed by electron microscopy were very small and quite different from our findings after hypertonic saline Our in vitro experiments demonstrated that only a very short exposure (½ hour) to hypertonic solutions is required to produce impressive histologic al changes The intensity of the damage corresponded to the concentration of NaCl used The changes produced *were similar to those seen in placentae obtain* ed after HSIA The results of this experiment confirm that the alterations we found in the placentae after HSIA are mostly due to effects produced in the first hour after instillation and are not caused by autolytic processes during the interval between salt instillation and delivery of the placenta

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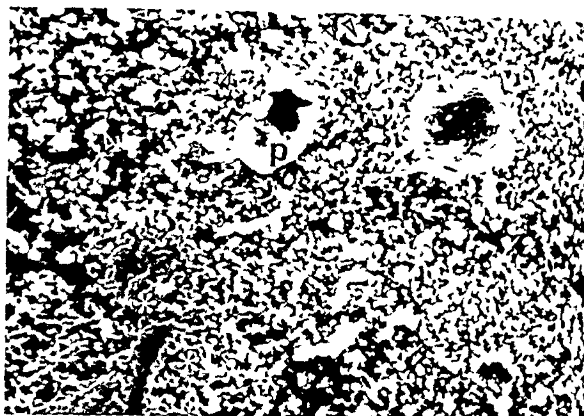


Fig 12 Scanning electron micrograph of part of a placental villus after in vitro treatment with 2½ per cent NaCl in SBSS for ½ hour Note the microvillous plaque ( ) the swelling of the tips of the microvili (arrows) and the [illegible] protrusions (*p*) × 19 000

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THE EVOLUTION OF CERVICAL MUCUS INFRASTRUCTURE IN NORMAL CYCLIC BABOONS (PAPIO ANUBIS) AND CASTRATED FEMALES RECEIVING HORMONAL SUPPLIES

A scanning electron microscope study

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bstract The scanning electron microscope was used to idy the evolution of the infrastructure of cervical mucus normal cyclic baboons and in castrated animals treated th ovarian hormones for establishing an artificial cycle both groups the results make conspicuous the progres- e enlargement of the filamentous woof which attains a ximum at midcycle and then decreases by degrees in the ond part of the cycle It was shown that the evolution of framework is very similar during normal and artificial le with only variations of slight amplitude Moreover the variations in the baboon mucus infrastruc e closely resemble those described in the human The re ts are briefly discussed in the light of known data

uated at the junction between the vagina and the rine cavity the cervical canal has a strategic posi n and constitutes a compulsory passage for sperm ls ascending from the vaginal seminal pool rough the medium of the mucous secretion pro- ed by its upper part it plays an essential role in reproductive process Indeed being easily netrable during the ovulatory period cervical cus is known to provide an almost impenetrable rier to sperms during the major part of the ovarian le The parallelism between changes in some ological properties of cervical mucus and varia ns in its penetrability by spermatozoa suggested t the phenomenon could be based on a mechanism ated at the macromolecular level That mechanism uld modify the mucus infrastructure as a result of rmonal influence

e physiological importance of cervical mucus its frequent involvement in human female sterili makes it essential to know its macromolecular rastructure The most plausible hypothesis concer ng the structure of the solid phase of cervical icus the so-called tricot like macromolecular gel angement was proposed by Odeblad (1968) But hough it seemed to provide the most satisfactory explanation for the rheological properties of cervical mucus as well as its cyclic obstructive characteristic and the changes in its chemical composition during the ovarian cycle Odeblad s scheme required confir mation

Due to its important depth of field and high power of magnification the scanning electron microscope *(SEM) yields a three-dimensional view of the spatial* arrangement of cervical mucus infrastructure and presents the tricot like macromolecular arrangement as a matter of fact (1 10) Recently the same technic permitted a study of the variations in cervical mucus framework throughout the ovarian cycle (7) during pregnancy or after menopause (4) and under in fluence of oral contraceptives (6) Consequently the filamentous three dimensional infrastructure of human cervical mucus appears now to be well established However the fact that human volunteers cannot be used for experimental purposes makes it necessary to use animals as similar as possible to the human model

In compliance with the taxonomic proximity of sub-human primates and man preliminary SEM studies have shown recently the striking similarity of human and baboon ovulatory cervical mucus (8)

This study was carried out in order to obtain fur ther insight into changes occurring in baboon cervical mucus during the ovarian cycle and to provide infor mation on the effect of exogenous ovarian hormones on the mucus infrastructure in the castrated baboon female

METHODOLOGY

Cervical mucus was obtained from six cyclic adult females (Papio anubis) selected according to three criteria
- good health
- absence of obvious cervical erosion
- satisfactory regularity of the ovarian cycle

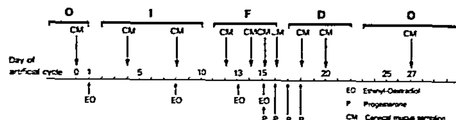


Fig 1 Artificial cycle ... castrated females.

To check the ovarian cycle each animal was followed for at least three months with a daily record of the sexual skin Mucus samples were taken every two days and correlated with the time of ovulation by first day of sexual skin detumescence which occurs in this species on the third day after ovulation (11)

Cervical mucus was also sampled from two females castrated at least 18 months earlier and given subcutaneous injection of 10 mg of Ethinyl-estradiol and 25 mg of progesterone (Luteogyl) according to a sequence that induces an artificial cycle (Table I)

Both cyclic and castrated baboons were anesthetized immediately before sampling using an intramuscular injection of Ketalar at a dose of 0.5 mg per Kg body weight Cervical mucus was aspirated from the endocervix by means of a Braun probe (1 mm in diameter) adapted to a 20 ml syringe *In order to reduce mechanical stress which could induce* distortion of structure in mucus samples the cervical secretion was aspirated very carefully and then evacuated slowly from the probe onto glass coverlips Only the samples which did not generate bubbles during sampling were prepared for SEM observation The specimens were immediately plunged into a fixative solution prepared extemporaneously (2 5 per cent of glutaraldehyde in 0 1 M Sörensen s phosphate buffer) rinsed in successive baths of buffer and distilled water then prepared for SEM by freeze-drying according to the process described previously in a technical paper (2) The observation was conducted with a Cambridge Mk II Stereoscan scanning electron microscope under an accelerating voltage of 25 kV

RESULTS

Normal ovarian cycle The SEM observation of a total of 224 mucus samples demonstrated the striking changes that occur gradually in the macromolecular framework of baboon cervical mucus through the ovarian cycle At the beginning of the menses period the glycoproteic filaments which constitute the mucus infrastructure appear to form a very compact mesh From that time the solid woof slackens progressively till the day of ovulation at which time the widening of the meshes reaches a maximum The reverse phenomenon occurs during the second part of the cycle The dimension of the meshes decreases by degrees whereas the woof density becomes more and more compact as the luteal phase goes on This evolution of the mucus framework involves important variations in both aspect and frequency of of structural filaments described previously (...

α filaments 4 000 to 2 000 A ϕ

β filaments 1 500 to 1 000 A°ϕ

γ filaments 750 to 500 A ϕ

The differences observed appear to be rarely ... cant from one day to the next except in the ... period Therefore the cycle was divided into ... periods (Fig 2)

Menstrual period (Phase +) During the menses, density of the meshwork seems to depend on ... portance of bleeding While the woof may ... be very compact in areas containing re... blood red cells (Plate I Fig c-d) the ... very large and the filaments fairly stretched ... conditions (Plate 1 fig a b) Ti... ments constitute the main part of the woof ... generally appear to be thick and short ... distorted by median or lateral thicknesses due probably to the lytic action of menstrual b... in bloody areas they may be long and smooth, ... out apparent distortion (Plate I Fig b) ... *are very rare and γ filaments only occasional*

Period of sexual skin intumescence (Phase I) A... very beginning of this period which can last ... to 12 days depending on the animal cervical ... exhibits generally a very compact meshwork co... ed of short and puffed β filaments (Plate II Fi... The woof tends then to loosen progressively ... ducing a significant increase in the dimension of ... meshes (Plate II Fig c-d) Actually the mesh...

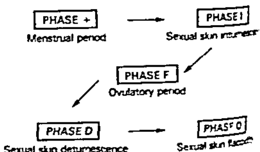


Fig 2

e I *Normal cyclic baboons*

	Menstrual period	Phase I	Phase F 1/3	2/3	3/3	Phase D	Phase O
f density	depends on bleeding	+ + + −	+ +	+	+ +	+ + +	+ + + + +
s of filaments							
			−	−	−	−	−
	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +
	+	+	+ +	+ +	+ +	+	+
cts of filaments							
ooth		−	+ + +	+ + + + +	+ + +	+	
ckled		−	+	+ +	+	−	
aight	+ + +	+ +	depends on constraints			+ −	+ + +
clots	+	+				+	+ +

vary from 0 5 μmm immediately after the menses o 5 μmm at the end of the intumescent period evolution of the structural filaments is no less ificant the β filament which are by far the most ierous appear to elongate progressively (Plate II b) Finally they may attain noticeable length (up 4 5 μmm) At the same time the median knesses specific for the previous period tend to ow and their number to decrease whereas thin al appendicules appear gradually on the β fila ts as time passes By contrast the frequency of α β filaments does not appear to differ much from of the menses period

od of full development of sexual skin (Phase F) engthening the β filaments the process of mesh rgement follows its course until the day of ovula (Plate III Fig a b) At this time the meshes at their largest dimension which may exceed 12 ı Concomittantly the surface of the oproteic filaments tends to become perfectly oth and isodiametric along their whole length te IV Fig a b) On the day of ovulation there are onger any median or lateral nodosities protruding n the β filaments except for occasional appen les which probably correspond to the stem of e broken lateral filaments (Plate IV Fig c-d)

process begins immediately after ovula the interstices of the meshes delimited by the oproteic filaments are seen to tighten progressive while thicknesses and appendicules reappear on β filaments which begin to shorten The laments are now more frequent but the frequency oth α and β filaments appears to be unchanged ite III Fig c-d)

As in the human two different three-dimensional arrangements can be observed which seem to be dependent on the physical constraints one can impose on fresh mucus during sampling When these con straints are sufficiently slight to be counteracted by the thickness and plasticity of the mucoid material lines of force cannot be produced to align the fila ments in a particular pattern The weft is therefore similar in appearance to an entangled skein of string and the meshes do not appear as large as in reality On the other hand when the mucus adheres to the coverslip before it is detached from the probe or if it has been subjected to strong constraint such as an appreciable elongation most of the filaments are oriented so as to be grossly parallel with the lines of force In that case they may constitute a thin struc ture that resembles a spider s web and the meshes appear to be larger than in reality

Period of sexual skin detumescence (Phase D) This fourth part of the baboon ovarian cycle has a short duration which may vary between 3 and 5 days depending on the animal Concomittantly with the in crease of sexual skin flaccidity during these few days the process of mesh tightening becomes more and more obvious At the end of the period the mucus framework appears to attain its highest density (Plate V Fig c-d) In some cases the weft is so compact that meshes can scarcely be distinguished Once more the medium size filaments constitute the major part of the solid phase of cervical mucus they are always very short and often form bloatednesses of varied size and shape (Plate V Fig b) The dimension of the meshes they delimit rarely exceeds 1 μmm In thin marginal areas submitted to stretching action the

Table II *Artificial cycle*

	deprivation	Hormonal Phase I	Phase F 1/3	2/3	3/3	Phase D	Phase O
Woof density	+ + + + +	+ + + −	+ +	+	+ +	+ + + −	+ + + +
Types of filaments							
α		−	+	+	+	−	
β	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + +
γ	−	+	+ +	+ +	+ +	+	−
Aspects of filaments							
smooth		+	+ + +	+ + + + +	+ + +	+	
buckled			+	+ +	+ −	+	
straight	+ + + + +	+ +	depends on constraints			+ +	+ + + +
+ clots	+ +	+					+ +

filaments often appear to be puffed up by median distortions and lateral appendicules (Plate V Fig a) The other types of filaments are still rare

Period of sexual skin flaccidity (Phase O) This period which precedes the next menses is the last and also the longest of the baboon ovarian cycle Its mean duration in our animals was about 10 days Compared with the former period the sexual skin is now absolutely flat During phase O the woof density attains its maximum and the compactness of the mesh may be compared with that observed at the end of the menses period (Plate VI Fig b-c d) Consequently the mesh dimension rarely goes beyond 0 4 µmm

However the α filaments are almost absent and the γ type more frequent at the beginning of phase O In addition the bloatednesses and clots distorting the filaments also appear to be more numerous (Plate V Fig a d) To clarify these results the most significant data concerning the evolution of the solid phase of baboon cervical mucus are summarized in Table I

The effect of exogenous ovarian hormones on cervical mucus framework of castrated females The results obtained in castrated females treated with exogenous ovarian hormones are very similar to those observed in cyclic animals (Table II) During each period of the artificial cycle the evolution of the structural filaments appears to be grossly parallel to the variations exhibited by the framework of cyclic mucus during the corresponding period

Indeed with the exception of midcycle during which the glycoproteic filaments do not appear as perfectly smooth in castrated animals the evolution of the mucus framework in cyclic and castrated baboons seems to be so similar that it would be difficult to make a clear distinction

During the period of hormonal deprivation density of the woof appears to be extreme (Pla… Fig a b) The appearance of the framework is … similar to that of the end of phase of sexual … cidity (Phase O) when hormonal supply … effective (Plate VIII Fig c d) In both … β filaments which constitute the major part of … mucus infrastructure during the whole cycle … pear to be extremely short and distorted by … and terminal nodosities The meshes they … rarely exceed 0 4 µmm As soon as the third … sexual skin intumescence (Phase I) the … of the meshes becomes visible in certain areas of … samples (Plate VII Fig c d) The mesh widening … tinues until the middle of phase F (sexual skin development) which appears to correspond … day of ovulation in normal cyclic animals (Pl… Fig a b) That phenomenon which induced … comittant elongation and smoothing o… filaments will then be reversed so that … again extremely compact some days after … ning of phase O (Plate VIII Fig c d)

Concerning the mesh dimension and the … pearance of the filamentous woof the similar… tween the true ovulatory period and the mid… phase F induced in castrated females appears … ticularly clear Indeed with the exception of … median nodosities puffing up the β filame… ovulatory type mucus of castrated baboons … medium size filaments appear to have in the … almost the same appearance length and size … normal animals The median nodosities are … casional and the structural filaments exhibit a … surface on the major part of their length The … pendicules one can observe here and there … the filaments probably originate … some joining γ filaments

DISCUSSION

close resemblance in both appearance and evolu of cervical mucus infrastructure in cyclic baboon in the human is hardly surprising in view of their taxonomic proximity This similarity which ap- s to be logical is particularly interesting from an rimental point of view one has a model as close ossible to the human which in the field of cer physiology permits many experimental ap- ches that for evident reasons would not be ible with human volunteers

e quasi parallelism in the evolution of baboon ical mucus framework during normal and ar ial cycles is no less important Being able to pro- at will ovulatory and then luteal pictures he mucus of castrated baboon by injecting diol and progesterone clearly shows that the sis of the observed filamentous infrastructure lies ormonal stimulation and does not result from nical manipulation

is not within the scope of this paper to discuss the nical aspects of cervical mucus preparation and possible generation of artifacts the reader who es to pursue that subject further is referred to ough studies and discussions that appeared more ss recently (2 3 4 5) However some of the data ined in this study reinforce and confirm my ious results and therefore must be pointed out

he possibility of encountering in dehydrated ba n mucus samples two major spatial arrangements fferent as the quasi parallel alignment and the led skein can be accounted for by the plasticity of mucoid material and whether or not a stretching on is applied to it Since the alignment without kage of the filaments can be obtained only by ching the mucus prior to fixation and dehydra the filamentous structures observed must be sidered as evidently pre-existent with regard to the parative process Likewise the mucus plasticity onsible for local spatial rearrangements resulting ccidental physical constraints rules out the ac ate measurement of important parameters such as nber of meshes mesh dimension and length or in number of each type of filament Therefore bols must be used instead of numbers when ac nting for quantitative evolution

he presence of median and to a smaller extent ral nodosities on the β filaments in the ovulatory mucus of castrated baboon could be due to ex ive progestagenic influence

The fact that such nodosities and also clots can be observed also in human cervical mucus during pregnancy and after menopause (4) and in the cyclic baboon during the menses period and phase O may be considered to favor that interpretation

In fact restoring exactly the physiological hor monal sequence in castrated animals can be con sidered a wager since many parameters interfere some of which cannot be controlled

Considering the greater length of the baboon sper matozoon compared to that of the human (9) and the similarity of cervical mucus factor in both cases one might suppose that sperm migration encounters greater mechanical obstacles in the baboon But such a conclusion must not be infered the sperm head has a similar dimension in the two species and the greater dimension of the tail could rather be a facilitating fac tor

ACKNOWLEDGEMENTS

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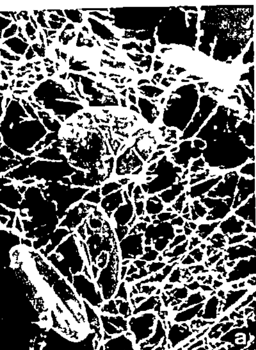
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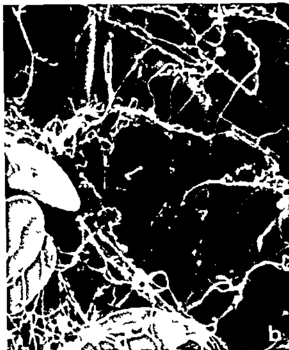
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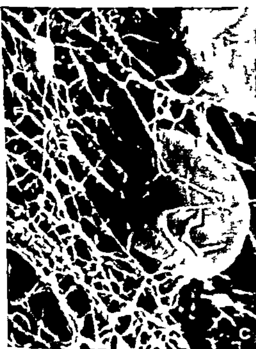
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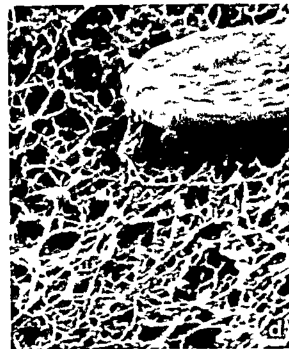
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e 1 Normal cycle Menses period (a) 1st day
nerous blood red cells are enmeshed in the filamentous
f which appears to be fairly slackened ×4500
1st day Margin of a very bloody sample The filaments
be distended giving this area the aspect of ovulatory
meshwork ×4 400

(c) Last day of menses period Despite the presence of some red blood cells the woof appears to be very compact The filaments are distorted by numerous median nodosities ×10 000

(d) Last day of menses period Note the extreme density of the meshwork at the surface of which a red cell seems to be floating ×10 000

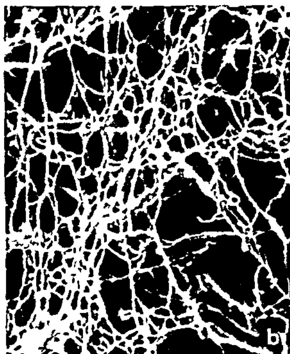


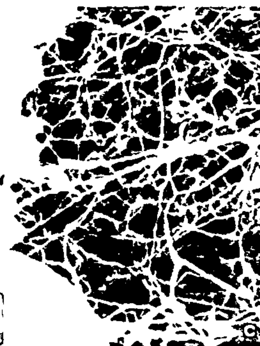


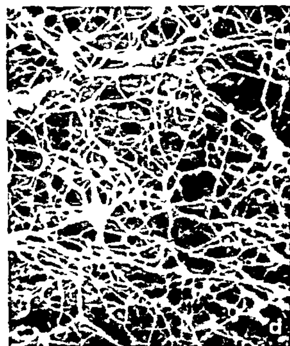


Plate II. Normal cycle Ovulatory period
(a b-c-d) The mesh exhibits meshes of very large dimensions Note the almost perfect smoothness of the filaments and the absence of nodosities Some broken junction filaments may be seen laterally to some filaments (arrows) Some clots can be observed (large arrows) These formations which are exceptional during the ovulatory where observed in only two females × 5 700 (for all p



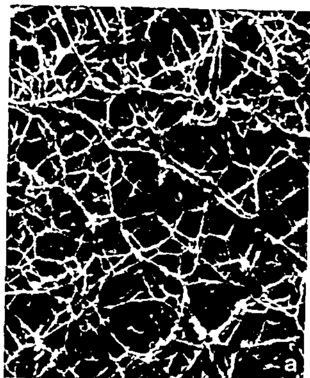






ate V Normal cycle Phase D (sexual skin detumescence) 2nd day of phase D Marginal area of a sample submit d to accidental traction force Note the clots and dosities puffing up the filaments and the cobweb-like ar ngement ×5 000

(b) 4th day of phase D ×7 000
(c-d) 9th day of phase D Note the tangled aspect of the woof A red blood cell is visible in figure c Fig c ×7 100 Fig d ×5 400



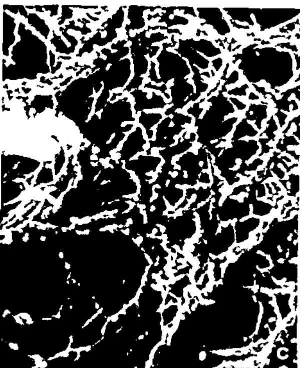
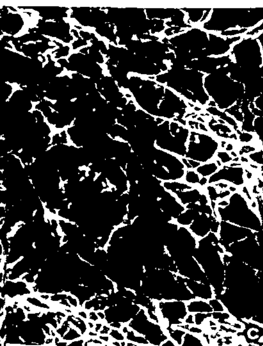
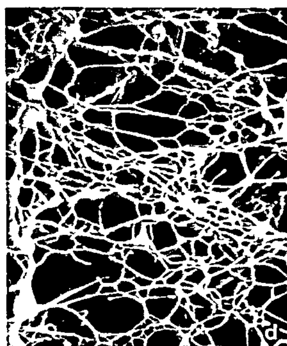


Plate VI Normal cycle Phase O (sexual skin flaccidity)
(a) 2nd day Clots and nodosities are now frequent ×5 000
(b) 4th day Note the extreme density of the woof and the very small mesh dimension ×7 850
(c) middle of phase O (6th day) ×7 900
(d) Last day of phase O (10th day) Some red b[illegible] and keratinized cells are trapped the woof ×8 00[illegible]









te VII Treated castrated baboon
period of hormonal deprivation Note the extreme den
y of the woof ×12 000
) period of hormonal deprivation Numerous nodosities
clearly visible ×12 000

(c) 3rd day of period of sexual skin intumescence (phase I) ×7 200
(d) 3rd day of phase I Numerous clots distort the filaments ×7 400









Plate VIII Treated castrated baboon
(a b) Midcycle period (phase F) Note the ovulatory type arrangement and the presence of nodosities on the filaments ×5 000 for both pictures

(c) 2nd day of phase O (sexual skin flaccid) meshwork has tightened considerably ×12 700
(d) 22nd day of phase O The woof is now extremely and compact ×12 200

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PERIHEPATITIS IN PELVIC INFLAMMATORY DISEASE — ASSOCIATION WITH INTRAUTERINE CONTRACEPTION

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bstract The Fitz Hugh Curtis syndrome (FHCS) or epatitis as a complication of pelvic inflammatory sease (PID) is readily diagnosed by laparoscopy Among 4 non selected cases of acute PID verified laparoscopical FHCS was found in 38 (13 8 per cent) Twenty four of e patients presented right upper-quadrant pain and nderness while 14 experienced no local symptoms Peri patitis was found in a slightly higher frequency in PID ses of low age and in those using intrauterine contracep- n (IUCD) but the differences lack statistical significance owever acute PID occurring within 6 weeks after IUCD ertion was associated significantly more often with ICS ($p < 0.01$) It is suggested that the traumatizing effect IUCD insertion facilitates the spread of pelvic inflam tory material to the perihepatic region

clinical picture of gonococcal peritonitis of the part of the abdomen was first described by Sta o in 1919 (7) In 1930 Curtis (2) reported the fre nt association of violin string or band adhesions een the anterior surface of the liver and the ietal portion of the peritoneum with coexistent ococcal inflammatory disease in the female pelvis clinical presentation of this syndrome was acterized by Fitz Hugh in 1934 (3) Most patients nt with the sudden onset of right upper rant pain and tenderness occasionally asso- d with a transiently non functioning gallbladder abnormalities of liver function and a perihepatic ion rub Histologically examination of liver sies reveals superficial capsular inflammatory tion without parenchymatous changes

he aim of the present study was to determine by roscopy the frequency of FHCS in a general PID- rial and possibly relate this to other parameters as age of the patient and contraceptive practice

MATERIAL

material consists of 274 cases of PID treated in Gynecological Department Aker Municipal Hos Oslo in the period January 1 1976 to December 31 1977 In all cases the diagnosis was verified by laparoscopy which also comprised an inspection of the hepatic region As to clinical appearance 24 patients complained of right upper-quadrant pain and tenderness of sudden appearance 14 of them were admitted to hospital within 48 hours Twenty-one patients were primarily admitted to a non gynecological department (mostly surgical emergency) The diagnoses on admission are shown in Table I The pelvic symptoms dominated in only four patients

RESULTS

Thirty-eight (13 8 per cent) of the 274 PID cases showed signs of perihepatitis i e patchy fibrine or purulent deposits on liver surface increased vascularization or hemorrhages in the subdiaphragmatic peritoneum In four of the cases the changes appeared to be of older date i e violin string or band adhesions but in these cases inspection of the pelvic organs revealed both acute inflammatory changes and evidence of earlier PID (adhesions)

In 14 patients with PID perihepatitis was diagnosed laparoscopically without symptoms from this region Generally the local reaction on the liver surface in these cases was less pronounced in most of them a fibrinous exudate was observed The severity of their pelvic affection — as estimated from the degree of visualized inflammatory changes general symptoms and erythrocyte sedimentation rate — did not differ from those with symptom bearing perihepatitis

Age distribution Table II presents the frequency of FHCS related to the number of patients with PID in different age groups The frequency is somewhat higher in the lower age groups (below 25 years) but the difference is not significant ($0.05 < p < 0.10$)

Intrauterine contraception Of the 120 PID patients using IUCD 22 (18 3 per cent) showed perihepatitis

Table I *Primary diagnosis on admission to hospital*

Diagnosis	No of patients
Cholecystitis/cholelithiasis	8
Abdominal emergency	7
Appendicitis	4
Liver abscess	1
Pelvic inflammatory disease	4

Table II *Appearance of Fitz Hugh Curtis syndrome (FHCS) related to the number of patients with PID in different age groups*

Age groups (years)	Frequency of FHCS in PID patients
15–29	15 4 per cent (10/66)
20–24	19 1 per cent (18/97)
25–29	10 9 per cent (7/65)
30–	6 7 per cent (3/46)

compared to 16 (10 4 per cent) of the 154 PID patients not using IUCD This difference is not statistically significant ($0.05 < p < 0.10$)

However when the duration of IUCD use is taken into account (Table III) it is found that the incidence of perihepatitis is significantly higher in the patients who developed PID shortly after IUCD insertion (i e within 6 weeks) than in other PID patients using IUCD ($p < 0.01$)

DISCUSSION

The etiology and pathogenesis of FHCS have not been elucidated Originally *Neisseria gonorrhea* was incriminated as being the only etiological agent Recently the syndrome has been observed in non gonococcal PID as well (2) Our material cannot resolve this question because bacteriological examination was not performed in all cases But it seems to us that the role of gonorrhea in the development of perihepatitis has been somewhat overestimated

The pathogenic agents have been thought to pass from the Fallopian tubes into the paracolic gutters of the abdominal cavity and then to the subphrenic spaces Recent reports of similar infections in the male (4 6) suggest other routes of dissemination such as hematogenous or retroperitoneal lymphatic spread

The Fitz Hugh Curtis syndrome is found in 1–10 per cent of cases with PID (2) Tenderness in the hepatic region has been observed in 31 per cent (2) The frequency of the syndrome will depend on the criteria used for the diagnosis of both perihepatitis and PID

According to modern opinion laparoscopy is the most reliable diagnostic procedure in cases where PID is suspected (5) We have found laparoscopy superior also in the diagnosis of perihepatitis The search for perihepatitis has in fact become a routine supplement to the ordinary laparoscopy in pelvic disease W[illegible] the patient in a horizontal position and the scop[illegible] serted transumbilically, the upper part of the [illegible] dominal cavity is readily visualized

The presentation of symptoms (right upper q[illegible] rant pain and tenderness) seems to be a quest[illegible] the quantity of the local reaction Less prono[illegible] perihepatic inflammatory changes are frequen[illegible] laparoscopically in cases lacking local symptoms

Weström (8) has reported a higher risk of PI[illegible] women using IUCD Whether FHCS is partic[illegible] associated with IUCD is questionable In our ma[illegible] the syndrome was found in a somewhat higher fre[illegible] quency in the PID patients with IUCD than in t[illegible] without (18 3 per cent and 10 4 per cent respectiv[illegible] but the difference lacks statistical significance

The procedure of IUCD insertion seems to [illegible] factor in the development of perihepatitis PID [illegible] pearing shortly after IUCD insertion i e wi[illegible] weeks were associated significantly more often [illegible] this syndrome A possible explanation might be the traumatizing effect of IUCD insertion fa[illegible] the spread of pelvic inflammatory material to [illegible] perihepatic region The present study cannot de[illegible] mine whether this takes place by the lymph[illegible] hemotogenous or direct intraabdominal route

ACKNOWLEDGEMENT

The author is grateful to Dr H Gjønnæss for valuable [illegible] vice and to colleagues for performing the laparosc[illegible]

Table III *Appearance of FHCS related to interval from IUCD insertion until PID development*

Duration of IUCD use	Frequency of FHCS in PID patients
Less than 6 weeks	42 8 per cent (15/3[illegible])
More than 6 weeks	8 2 per cent (7/[illegible])

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Date	Place	Name	Office
1980			
May 21	London England	Symposium on Tubal Infertility	Inst OB/GYN Queen Charlotte's Maternity Hospital Goldhawk Road London W6 OXG England
May 26–28	Viareggio Italy	International Symposium on the Menopause Endocrinological & Pathophysiological Aspects	Serono Symposia Via Ravenna 8 I–00161 Rome Italy
May 27–31	Hamburg Germany	International Congress on Senology	H J Frischbier Universitäts-Frauenklinik Martinistr 52 D-2000 Hamburg 20 Germany
June 9–12	Gothenburg Sweden	XXI Congress of The Nordic Association for Obstetrics and Gynecology	Dr Hans Bergström Dept OB-GYN Sahlgrenska Hospital S–41345 Gothenburg Sweden
June 9–12	Ostend Belgium	Third International Congress on the Menopause	Int. Menopause Society 8 Av Don Bosco B–1150 Brussels Belgium
June 16–20	Florence Italy	XI International Congress of the International Society of Psychoneuroendocrinology	Fondazione Giovanni Lorenzini Via Monte Napoleone 23 I–20121 Milan Italy
June 17–19	Budapest Hungary	International Symposium on Computer aided Diagnosis in Perinatology	Secretariat of the Congress of Comp aided Diagnosis in Perinatology Mr Z Katona 1055 Budapest Kos Lajos tér 6-8 Hungary
June 30	London England	Progress in Neonatal Medicine	Symposium Secretary Institute of O and Gynaecol Queen Charlotte's Maternity Hospital Goldhawk Road London W6 OXG England
June July 30–2	L Aquila Italy	International Symposium on Oligozoospermia	G Frajese Clin Med V – Policlin Umberto I – 00100 Roma Italy
June July 30–3	Leuven Belgium	Gynecological microsurgery A practical course	Dr W Boeckx Centre for Microsu Academic Hospital St Rafael 300 Leuven Belgium
July 3–5	Bordeaux France	International Symposium on IUD Technology	Dr Karl-Gösta Nygren University Hospital S – 75014 Uppsala Swede
July 4–6	Toulouse France	6th International Symposium on Sex Education	C I F R E S 17 Rue de Nimes 31400 Toulouse France
July 5–11	Madrid Spain	Xth World Congress on Fertility and Sterility	Congress Secretariat Calle San Bernardo 5 Madrid Spain
July 4–8	Rome Italy	Internationel Congress on Women and Sport	Scientific Secretariat International Congress on "Women and Sport" Piazza Mignanelli 4 00187 Rome It
July 8–11	Edinburgh England	22nd British Congress of Obstetrics and Gynaecology	Royal College of Obstetricians & Gyn cologists 27 Sussex Place Regent's P London NW1 4RG England
July 20–23	Williamsburg USA	AAGL Laparoscopic sterilization A comparison of the methods	American Association of Gynecologic Laparoscopists 11239 South Lake D Downey California 90241 USA

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VAGINAL YEASTS IN PARTURIENTS AND INFESTATION OF THE NEWBORNS

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act Vaginal yeasts from 992 full term pregnancy par its in the delivery room were cultured and identified s were similarly cultured from the mouth of the orns seven days after birth to find out whether a viable infection had taken place Anamnestic data concern mital infection earlier or during the present pregnancy collected from the parturients The yeast findings are ared with results from similar cultures from gyne ic out patients

ginal yeast infection had been diagnosed before the nt pregnancy in 16 5 per cent and in some phase of the nt pregnancy before the delivery in 8 5 per cent of the rients A positive yeast culture with no clinical symp- during the pregnancy was found in 9 9 per cent cal symptoms were present in 61 per cent of the yeast re positive parturients

ogether 3 155 specimens were studied and 670 yeasts identified Positive yeast cultures from parturients obtained in 23 7 per cent and from gynecologic pa in 30 9 per cent Candida albicans was the most com yeast It was followed by Saccharomyces cerevisiae in arturients and Torulopsis glabrata in the gynecologic nts Pityrosporum ovale/orbiculare was also common e latter material S cerevisiae as well as Pityrosporum es are usually not identified in the medical yeast atories for methodological reasons

sitive yeast culture from the mouth of the newborns obtained only in 20 cases A symptomatic oral can sis was not present in any of the cases

ports vary concerning the frequency of vaginal ida infection during pregnancy The figures lly range between 17 and 50 per cent depending e methods used and the kind of material studied findings reported during the last few years have compiled in many papers (5 6 8 16) Similarly are variations in the reported frequencies of ptoms due to candida infection (candidosis or lidiasis) The most common figures state that ½ of the patients are symptomless Comparative ies on fungus infestation in mother and child shown unequivocally that the infected birth l represents the principal source of infection for the infant Smidt (20) and Holltorff *et al* (10) discovered vaginal candidiasis in the mother in 85 per cent of newborn babies with yeast infections Careful studies by Blaschke Helmessen (1) showed that Can dida albicans strains detected simultaneously in the mother and child are culturally identical While all in vestigators agree that Candida albicans is the most common yeast isolated from vagina there are con siderable differences in the reported frequencies of other yeasts For example Torulopsis glabrata is hardly mentioned by some investigators while it *comprises up to 30 per cent in other studies (24)*

The purpose of the present study was to determine the frequency of candida in the vagina of full term pregnancy women admitted to delivery room in our Central Hospital The yeasts have been cultured in order to identify the infestating yeast species Yeast cultures have also been carried out from the oral cavi ty of the newborns one week after birth in order to find out to what extent viable transfer of yeasts takes place during birth The frequency of the various yeast species in the vaginal samples are compared with results collected from gynecological outpatients of our hospital

MATERIAL AND METHODS

The number of mothers was 992 The youngest mother was 16 and the oldest 45 years-old most belonged to the age group 25–29 years They were carefully asked about episodes of vaginal discharge and vulval symptoms possible medication used etc Samples were taken from the middle part of the vaginal wall after the women had been admitted to the delivery room at the beginning of labor The samples were taken with loop directly to fungal culture medium Dixon s yeast medium was used and the culture was carried out immediately at 37 C for three to seven days Samples were collected in the period 30 12 1977–8 5 1978 at our University Central Hospital

Samples were similarly collected from the mouth mucous membrane of the infants seven days after delivery while still in hospital Cultures were made immediately in the

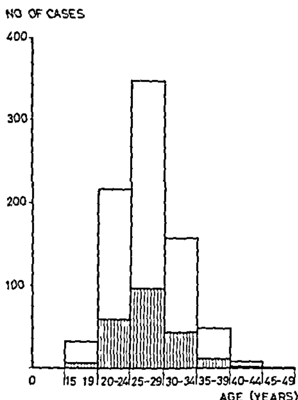


Fig 1 White columns age distribution of all parturients dark columns age distribution of yeast positive

medium in exactly the same way as from the mothers Identification of the yeast was carried out according to Lodder (13)

RESULTS

Medically treated vaginal discharge and/or vulval symptoms at some time earlier was registered anamnestically in 25 9 per cent and during the present pregnancy *before delivery* in 12 2 per cent A diagnosed vaginal yeast infection was registered some time before the present pregnancy in 16 5 per cent and during it in 8 5 per cent These patients had had typical discharge redness and genital pruritus which had led to a medical consultation

The yeast cultures of the parturients taken *in the delivery room* were negative in 756 and positive in 236 cases i e a positive culture was found in 23 7 per cent of the total of 992 parturients In 61 0 per cent of these there had been symptoms during the pregnancy A positive yeast culture with no clinical symptoms during the pregnancy was found in 9 9 per cent of the parturients The yeast species identified are listed in Table I As expected the most common isolated species was Candida albicans The high freque Saccharomyces cerevisiae is noteworthy

A yeast culture was obtained from 821 801 of them turned out to be negative Th positive cultures or less than three per cent amount (Table I) Again C albicans was th common species identified In six of these C cases the culture from the mother s vag tive which means that the source of yeast mother s vagina Clinical signs of oral were not found in any of the infants at the ti sampling

The age distribution for parturients with vaginal yeast culture was similar to that for a parturients as seen in Fig 1

For comparison Table I also includes our yeast finding in gynecologic patients the outpatient department of the same hospital seen that a positive culture was obtained from per cent of the cases The most common C albicans but the high frequency of T compared to the few findings of this species parturients is to be noted Another ding is the relatively high frequency of P (including ovale and orbiculare) in the patients compared to the parturients

DISCUSSION

The method of collecting specimens culture media and carrying out the mediately can be expected to yield the most data about the frequency of vaginal yeast in It was shown for instance by Timonen et that in a material of 10 344 patients only seventh of cases of mycosis can be preparations made by Papanicolaou s stai que even when special attention is paid to yea tures Holmberg and Laudanska (9) found y cytology material from a health control survey 3 3 per cent According to Thomsen Peder Bach (23) microscopy of the vaginal samples smears seldom revealed a diagnosis with e PAS-staining and addition of potassium 10 per cent concentration led to suspicion c didiasis in only about half of the cases Meth these have been used in some of the earlier inv tions without cultural verifications which plain some of the great variations in the f reported

ble I *Yeasts identified in vaginal samples from parturients and in the mouth mucosa of their infants one we later For comparison are given yeast findings in gynecological patients from the same hospital*

-dentified	Present study Mother	Infant	Gynecologic patients	Total
dida albicans	171	15	263	449
dida guilliermondii	1	0	0	1
krusei	0	0	10	10
dida parapsilosis	1	1	9	11
rugosa	0	0	1	1
dida tropicalis	0	0	2	2
m	3	4	50	57
dotorula sp	0	0	1	1
haromyces cerevisiae	52	0	25	77
glabrata	7	0	53	60
hosporum cutaneum	1	0	0	1
al	236	20	414	670
ture negative	756	801	928	2 485
al	992	821	1 342	3 155

Sauramo and Penttinen (17) using yeast cultures mycosis in 25 per cent of pregnant women ularly they found mycosis in 25 per cent of ecologic patients with vaginal discharge In a es of gynecologic patients Timonen *et al* (24) nd vaginal yeast infection in 35 5 per cent Var ien and Tervilä (25) found vaginal mycosis in 28 cent of primiparae during the time of delivery finding of 23 7 per cent in parturients at the time lelivery and 30 9 per cent in the gynecologic pa ts are well in line with these results This suggests the prevalence of candidosis during pregnancy not increased markedly during the past decade or n this part of the world This would agree with mberg and Laudanska (9) who found no proof l general increase in candidosis in a Swedish ulation

rom other parts of the world the frequency of 0 per cent for vaginal candida infection during last trimester of pregnancy is often cited (5 16) figure has remained at the same level for years ough still higher figures have been reported (18) frequency of positive cultures rises with the dura of gestation Emir (4) found occurrences of 11 4 cent 13 3 per cent and 36 4 per cent for candida itis in the 1st 2nd and 3rd trimester of pregnan respectively In nonpregnant women the preval of vaginal candida infection is usually stated to around 11 13 per cent (19) higher figures are orted for users of contraceptive pills For normal ulations outside venereological clinics however real prevalence remains below that found during last trimester of pregnancy (15)

About one third to one half of those carrying can dida infection are usually reported to suffer from vulvo-vaginal symptoms In our material about two thirds of the women with yeasts were considered symptomatic cases It is however to be noted that this refers to the symptoms throughout the pregnancy and not just those of the last few days or even of the last trimester alone

The age curve of the patients with a positive vaginal yeast culture was similar to that of the whole par turient material This shows that yeast infections are not prone to any particular age group Also Clark and Solomons (2) have shown that there is no definite variation in the frequency of candida vaginitis during the reproductive phase It has further been found that the incidence of vaginal mycosis is not related to age or parity (3 7 11)

The yeast species identified by us appear to be the same as those reported in most of the earlier studies C albicans being the most common The remarkable thing in our findings from the end of pregnancy is the small number of different species found in com parison to the gynecologic patients Torulopsis glabrata was seldom found among the parturients whereas it represents 13 per cent of the yeasts in the gynecologic material In some studies its frequency has been found to be even higher in the Finnish material of Timonen *et al* (24) it represented 31 per cent Several other reports hardly mention it This suggests that among gynecologic cases T glabrata is to be expected in a high frequency while in obstetric materials it is rare Whether this is due to special en vironmental vaginal conditions during pregnancy re

mains to be seen

Another noteworthy finding is the high frequency of Saccharomyces cerevisiae This species is also seldom mentioned in reports on genital mycoses and its role in causing genital symptoms is disputed some state that is is a commensal others that it is a pathogen The fact that it is often not mentioned among the yeast species found is clearly a consequence of the methods used It is easily overlooked as a candida species other than C albicans unless adequate fermentation and assimilation series are done and ascospores are searched for after adequate stainings This is seldom undertaken in medical mycological laboratories The fairly common finding of S cerevisiae in symptomless patients suggests that it has no pathogenic role However one occasionally meets patients who have recurrent genital symptoms and repeatedly only S cerevisiae can be identified in cultures In this material S cerevisiae appeared to be somewhat more frequent in the parturients than in the gynecologic patients

Another species which has hardly been mentioned in reports on genital yeasts is Pityrosporum ovale and orbiculare which many consider to be a single species This is due to the fact that Pityrosporum does not grow on the usual media for yeast culture We used Dixon s medium which allows growth of Pityrosporum and found it quite frequently in vaginal cultures Whether it is to any extent a pathogen is unknown

The yeast infected birth canal is stated to be the most usual site of infection for the newborn In some works this has been the subject of special studies and even 85 per cent of the infants born to yeast carriers have been claimed to be infected during birth (1) Much lower figures have however also been reported In our study the specimens from the mouth mucosa were collected 7 days after delivery with a view to determining the frequency of oral infection that was stable enough to cause candidosis In several other studies specimens have been taken immediately after birth when the mouth has certainly contained transient vaginal secretion which is no doubt eliminated very rapidly Consequently our finding of positive candida cultures from the mouth specimens was very small about 3 per cent And even these include several cases where the mother s vaginal culture was negative so that the source of infection was not her birth canal Other possible sources of yeast infection could be e g the mouther s mouth since the mouth of adults of that age is yeast infected in some 25 per cent Other sources could be the mou[illegible] hands of the nurces doctors and others who [illegible] of the babies Air food cloth bottles and [illegible] utensils may be minor contributors

According to Lachenicht *et al* (12) about [illegible] of the babies infected during birth later develop [illegible] of clinical oral candidosis It remains to be found in further studies whether this holds true in t[illegible] sent material Intertriginous cutaneous cand[illegible] the other relatively frequent consequence of candida infection Bronchopulmonary mycos[illegible] to aspiration of yeasts and infestation of gastrointestinal tract followed by digestive [illegible] bances are not so rare while more serious types [illegible] fection usually occur only in connection with [illegible] nological deficiency states

The symptoms of candidosis appear very s[illegible] the newborns of the yeast infected mothers, candidosis which requires treatment can be already on the fourth post partum day (10) [illegible] of our subjects could however a clinically oral candidosis be detected Any case of oral [illegible] didosis in the newborn is however often requires treatment In order to elimin[illegible] most frequent site of infection it has been that a vaginal yeast culture should be taken [illegible] gravida before the calculated delivery time ([illegible] 21 22) This is not done at present in contrary opinions about its necessity presented The same applies to the nystatin [illegible] axis of all newborns which some authors [illegible] quested (12)

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Date	Place	Name	Office
1980			
September 2–3	Barcelona Spain	Congreso Europeo Perinatal	VII Congreso Europeo de Medic Perinatal Apartado de Correos N 29015 Barcelona Spain
September 2–5	Barcelona Spain	7th European Congress of Perinatal Medicine	Congress secretariat Apt 29015 Barcelona Spain
September 2–6	Berlin Germany	6th International Congress of Psychosomatic Obstetrics and Gynecology	Ass Prof Dr M Stauber Fr . Charlottenburg der FUB Pulsst D-1000 Berlin 19 W Germany
September 4–7	Kiwah Island Charleston SC	International Symposium on Carcinoma of the Cervix Biology Etiology & Diagnosis	E S E Hafez M D OB/GYN State University Medical Res Bl 550 E Canfield Detroit MI 48
September 15–16	Bologna Italy	First International Symposium on Recent Advances in Prenatal Diagnosis	A C Assistanza Congressi Via l Palagi 21–40138 Bologna Italy
September 22–28	Varna Bulgaria	3rd International Colloquium on Physical and Chemical Information Transfer in Regulation of Reproduction and Aging	Bulgarian Academy of Sciences J G Vassileva Popova c/o Dept of Biophysics 113 Soph Bulgaria
September 24–27	Kiel West Germany	Embryo Transfer and Instrumental Insemination	Professor Kurt Semm Abteilun Frauenhei lkunde D-2300 Kiel 1 W Germany
Sept-Oct 29–1	Freiburg Germany	International Congress on Endocrinology of Human Infertility	C Ferrarri M D P O Box 995 Milan Italy
September 30	London England	Anti androgen therapy for hirsutism	Symposium Secretary Inst of Gynaecol Queen Charlotte Hospital Goldhawk Road W6 OXG England
October 3–5	New Delhi India	3rd International Seminar on Maternal and Perinatal Mortality Pregnancy Termination and Sterilization	Hon General Secretary The Fed Obstetric & Gynecologi . India Purandare Griha 31/c Dr N A Purandare Marg Bombay 400 007 India
November 14–17	Madrid Spain	7 Congrès Européen de Medecine Perinatale	Professor de la Fuente Maternidad de la Ciudad Av Generalissimo 177 Madrid 34
November 18–23	New Orleans Louisiana USA	Clinical Symposium on Gynecologic Endoscopy	American Association of Laparoscopists 11239 South Boulevard Downey California
November 20–22	Barcelona Spain	Symposium International Sobre Monitarizacion Prenatal	Instito Dexeus Srtas M Luis Ana Baldrich c/Paseo de 67 Barcelona 17 Spain
December 1–4	Kairo Egypt	Second Congress of the International Society for the Study of Hypertension in Pregnancy	Docent Hjördis Robbe Dept of Obstet and Gynecol. Karolinska Hospital S-104 01 Stockholm 60 Sweden
December 1–12	Melbourne Australia	Seventh UICC Training Course in Cancer Research	Dr A W Burgess UICC Course The Walter and Eliza Hall Inst Royal Melbourne Hosp P O Victoria Australia

ETIOLOGY OF PREMALIGNANT CERVICAL LESIONS IN TEENAGERS

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tract The etiology of premalignant cervical lesions was anamnestically in teenagers The material com ed of 54 patients (mean age 18 0 years range 12–19 rs) treated in 1973–77 Early coital practise and fre nt change of sexual partners were usual Previous abor s and frequent genital infections were also typical The ıg frequency of dysplasias in young age groups calls for general knowledge and information even among and if possible mass screening

974 we reported an increase of premalignant le s since 1968 in teenagers (8 9) Infection seemed ely cause but it was not possible to prove that a s was definitely responsible Since then the in se appears to have continued Table I and Fig 1 it could be the cause of this tendency?

MATERIAL AND METHODS

ned to clarify this problem anamnestically A careful ological history was taken from 54 patents aged ≤ 19 treated in 1973–77 The diagnosis moderate or dysplasia was based on histopathological examina at the Department of Obstetrics and Gynecology u University Central Hospital

RESULTS

The mean age of the patients was 18 0 years (range 12–19 years) Eleven patients were married Twenty two patients were students twenty belonged to the group of skilled labor or junior office employees seven were unskilled workers and five were higher office employees

The mean age of menarche was 12 7 years (range 10 –16 years) Thirty six patients had undergone previous gynecological examination at least once Vaginal smear had been taken from 24 patients Three patients had had gonorrhea 36 patients simple vulvovaginitis and five patients pelvic infection in their medical history

Coital practise had started at the age of 14 2 on average (range 11–18 years) The patients had had six partners on average (range 1–100 four of them had had ten partners two patients 20 and one patient over 100 partners Coital frequency varied between three times a year and many times a day the most common being twice a week

Six patients had never used any preventive method Forty patients relied on condoms Pills were used by 28 patients (16 used mini pills 12 had combined pills) two patients used foam one patient had an IUD The duration of use varied between two months and several years Ten patients had had one delivery

…e I Premalignant cervical lesions in teenagers in the Department of Obstetrics and Gynecology Turku …ersity

	Total amount of dysplasias	Dysplasias at age ≤19 years	
		No of cases	Per cent
–69	85	4	4 7
–71	130	3	2 3
–73	127	16	12 6 ($p<0\ 01$)
–75	68	15	22 0
–77	89	35	39 3
	499	73	14 6

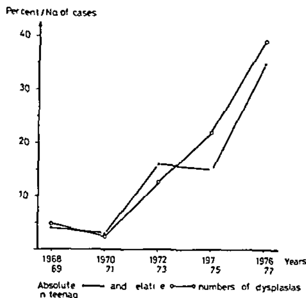


Fig 1 The rising frequency of dysplasias in young age groups

two patients two deliveries one patient had under gone two spontaneous abortions and a legal abortion had been performed in ten patients

DISCUSSION

An increase of premalignant cervical lesions in teenagers has been verified by several authors (1 2 3 8 9) Two etiological theories have been presented early coital practise and frequent change of sexual partners In our material the mean age at the first sexual intercourse was 14 2 years while the usual rates among the Finnish female population are 19 3 years in women born in 1942–46 18 8 years in those born in 1947–50 and 18 1 years in those born in 1951–53 (10) The decrease in age at first sexual intercourse was distinctly faster than the decrease in the age of sexual maturity Considering the young age of the patients in our material we must also pay attention to *the number of sexual partners (6 on the average)* Sievers *et al* (10) have reported that 4 per cent of the unmarried Finnish women in age group 18–29 years had had ≥ 10 sexual partners and 16 per cent had had 4–9 partners

Two clinical factors are present in the vast majority of young patients with cervical premalignant lesions sexual promiscuity and contraceptive pills (5) In our own material more than half of the patients use pills Therefore it is understandable that they have higher sexual activity and higher incide cervical ectopy as shown by Moghissi (6) Acc to Leppäluoto (4) it may be inferred that both i miscuous young women and in young women i pill the increased incidence of cervical metaplas ectopy plus the active sex life are likely to incre possibility of a chance hit between coitus-asso carcinogen and the target cells Clinically an c ed number of women with suspicious Papa.x smear and with ' surface dysplasia would l pected to emerge from the two groups of you.g en

Previous abortions and frequent genital inf of various types were typical in our material I earlier material the frequency of cytomegalov tibodies was the same as in a healthy popula.c H V H 2 frequency was a little greater b difference was not statistically significant (9) (other hand in patients with cervical cancer h *found distinctly increased amounts of H V H* bodies (7) The possible role of infection as a however needs further study

The Scandinavial Association of Obstetric Gynecologists (11) recommends that the mass ing programs should be continued and especially at risk groups However because cidence of cervical carcinoma in the age group ied has significantly decreased at the same tim number of *dysplasias in younger age group* creased we should seriously try to increase knowledge and information in the latter a and ensure that the mass screenings reach the We definitely agree with Leppäluoto (4) wh

From a clinical point of view the restorat healthy cervical epithelium and a healthy vagi tent would serve as a prophylaxis for malignancy

ACKNOWLEDGEMENT

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CASE REPORT

PRENATAL DIAGNOSIS OF OMPHALOCELE BY ULTRASOUND AND AMNIOGRAPHY

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phalocele is a herniation of viscera into the base .he umbilical cord with a covering membranous of peritoneum amnion as opposed to umbilical ııa which is covered by skin (9) The umbilical l is insulated into the sac (6 11) Omphalocele esents a failure in the normal developmental ıts before the tenth week The incidence varies n one of 3 200 to 10 000 live born infants (3 9) associated anomalies vary in reported series from o 50 per cent or more In a survey of 236 cases ore (10) found 38 per cent The malformations are ıly intestinal defects but non jejunoileal in con to malformations in gastroschisis (10) Most pa .s have incomplete rotation and fixation of the gut (9 10) Severe cardiac malformations are fre ıt (Moore (10) 20 per cent) and omphalocele n plays a major part in specific syndromes (9) ıy but not all infants are premature

hromosomal abnormalities seem to occur with in sed frequency (11) Lately reports have linked ıotic and serum fluid alpha fetoprotein elevation ı fetal omphalocele (1 2 4 7 13 1 4) and poly ramnios is almost invariably related to the ence of the malformation (8 14)

rdinary radiographs rarely reveal soft tissue en ements while amniography is a most useful tool letect fetal malformations Within the last year e reports of intrauterine diagnosis of omphalocele ıltrasonography have been published (3 4 5)

his paper is a report of an omphalocele diagnosed ıtero with ultrasound scanning and amniography with concurrent values of plasma estradiol and ıma placental lactogenic hormones recorded sma and amniotic fluid alpha fetoprotein values e measured and chromosome analysis was per ıned

CASE HISTORY

The mother a 33 year old woman gravida V para IV had no previous medical history or familial dispositions to malformations She had slight vaginal bleeding and contrac tions in the 11th 18th and 19th weeks of the pregnancy



Fig 1 1 Intestinal loops inside the omphalocele at the um bilical level
2 Omphalocele long axis 9 cm
3 Amniotic fluid



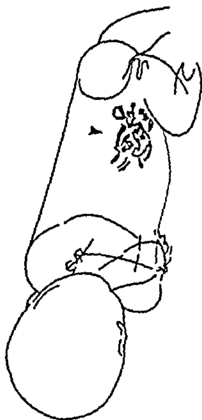


Fig 2 Amniography A p (Fig 2a) and lateral (Fig 2b) views with corresponding drawings of all visible surface structures of the female fetus Radiographs taken 24 hours after the injection of meglumini amidotrizoas (Urografin) 76 per cent 15 ml and lipiodol ethylique fluid (Lipiodol) 6 ml in to the amnion The water soluble Urografin is only visible in the fetal intestines (small arrows) while the oily lipiodol outlines the vernix coated fetal skin as a thin radiopaque film There is no visible contrast medium on the surface of the abdomen indicating either lack of coated skin or a non visible soft tissue process lying [illegible] contact with the abdominal surface The position [illegible] lowermost hand of the fetus (Fig 2a big arrow) [illegible] dicate that it rests on such a soft tissue process The direct signs were interpreted as a big omphalocele [illegible] ing no intestinal structures at the time of examin[illegible]

Two ultrasound scannings in weeks 11 and 19 showed no sign of a placenta previa or anything abnormal In week 4 polyhydramnios was obvious The uterus was equivalent to week 32 she had gained 15 8 kg in weight and her blood pressure was 135/90-160/110 She had light edemas The plasma alpha fetoprotein value was above normal She was treated with hydrofluomethiazidum (RONTYL[R]) and the edemas disappeared but polyhydramnios persisted A new ultrasound scanning revealed a well-defined omphalocele (Fig 1) and a fetus with a biparietal diameter of 7 3 cm An amniography was performed (Figs 2a and 2b) and supported the diagnosis of omphalocele but did not reveal any other malformations Amniotic fluid alpha fetoprotein however was significantly increased compared to our normal standard In order to prevent pre term labor the mother was treated with ritodrine chloridum (UTOPAR[R]) intravenously but 5 days later because of slight contractions she was transferred to the Department of Obstetrics at Rigshospitalet since the Herlev Hospital does not have a neonatal intensive care unit and division of neonatal surgery At this time four consecutive values of plasma estradiol and plasma placental lactogenic hormones within normal ranges

Two plasma alpha fetoprotein values were [illegible] creased A final ultrasound scanning estimated the fe[illegible] to 29 weeks (biparietal diameter 7 7 cm) One [illegible] contractions reoccured in spite of maximum dos[illegible] UTOPAR[R] The mother was given Betametasone [illegible] phosphate (CELESTONA[R]) 12 mg intramuscular[illegible] to prevent respiratory distress syndrome in the new[illegible] approximately 18 hours later a cesarean section wa[illegible] formed

A live girl weight 2 025 grams was delivered She [illegible] ed an Apgar score of 3 after 1 minute and 6 af[illegible] She had respiratory acidosis and after in[illegible] to a respirator in which she recovered fairly well [illegible] teral treatment was initiated at delivery A [illegible] omphalocele with amniotic covering protruded thr[illegible] umbilical ring 2½ cm in diameter (Fig 3) A few [illegible] loops were easily reposed into the abdomen and the [illegible] ligated at the basis and extirpated The remainder of [illegible] was covered with plaster





ss than 24 hours later the infant died because of cardial re with low blood pressure

uring these last hours the abdominal volume increased derably and puncture of the abdominal wall showed peritoneum An intravenous urography showed no ex m from the kidneys Autopsy diagnoses were Severe rrhage of the suprarenal glands pancreatic hyper renal infarction subarachnoidal petecchiae over the spheres and under the cerebral basis There were no of malrotation of the intestines The heart was very but otherwise normal The main vessels were nor The lungs contained little air and were voluminous

DISCUSSION

s case history illustrates developments in the atal diagnosis of severe malformations by using isticated techniques in ultrasonography and radi phy Close cooperation between the obstetric artment the ultrasound laboratory and the X ray artment should provide obstetricians with much er possibilities of predicting severe or lethal con ons in the fetus thus yielding the options of either inating a pregnancy before term in order to id delivery of an infant with such severe malfor ions that the chances of survival are nil or preparing for a delivery under optimal conditions so as to improve the infants chances of survival without further risks evolving from little knowledge of the prenatal intra uterine situation It also demonstrates however that even with a well substantiated set of in formation it is extremely difficult to predict the out come if a high risk pregnancy is allowed to continue

It could be argued that the risk of associated anomalies to omphalocele is so great (3 4 8 14) that if the diagnosis is made prior to week 28 or if possi ble week 20 as achieved by Campell *et al* (4) an abortion should be performed so as to spare the parents the tragedy of a child with malformations in compatible with survival for more than a short time

The development of severe hydramnios should al ways induce a thorough examination by a highly skill ed ultrasound technician or an amniography

Diabetes and RH immunization should be ruled out

From our case it seems that plasma estradiol and plasma placenta lactogenic hormone values do not give any indication of the diagnosis and although reports (1 2 4 7 13 14) of elevations of serum and amniotic fluid alpha fetoprotein in condordance with



Fig 3 Infant immediately after delivery

omphalocele have been published lately the available information is so sparse that it only serves to warn the obstetrician of omphalocele as one of the many serious prenatal conditions associated with this symptom

If however the omphalocele is diagnosed so late in the pregnancy that abortion is out of the question the utmost precautions should be taken to prolong the pregnancy until term in order to prevent the delivery of a premature child It has been shown (10) that 59 per cent are born prematurely or have low birth weights and the prevention of respiratory distress syndrome by prolonging the pregnancy administering betametasone to the mother and delivering by cesarean section should improve the newborn s chances of survival The infant must be warded in an intensive-care department with a neonatal surgery unit and the proper operative technique applied if repair of the hernia is absolutely necessary Here especially it is recommended to avoid opening the amniotic covering since this poses grave risk of sepsis (9 10) The reposition of a large hernial content into the abdominal cavity involves the risk of pushing the diaphragm high up into the thorax which will augment respiratory distress (12) In addition the increased content of the abdomen might create a compression of the inferior vena cava with blockage in the venous return diminished cardiac output and eventually shock and cardiac arrest

Other complications of overcrowding the a are impaired kidney function and intestinal c tions with pressure necrosis In all it seem nonoperative management of intact om hal especially valuable in premature infants with tic sac (9)

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CASE REPORT

RECURRENT URINARY INCONTINENCE TREATED NEUROSURGICALLY

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Neurogenic bladder dysfunction can be difficult to nage and is usually impossible to cure This case report neurosurgical treatment of a case of recurrent incontinence in a 56 years old woman who was pre ly treated on four occasions with vaginal repair opera ıs with no beneficial effect

Cystometry revealed detrusor hyperreflexia (supranuclear dder paresis) Myelography demonstrated cervical spinal d compression She was treated with spondylodesis of cervical spine with complete relief of incontinence 18 nths postoperative cystometry was normal and after ee years she was free of symptoms

urogenic bladder dysfunction is a known sign and nptom of many diseases such as multiple sclerosis Parkinson s disease (3) cerebral vascular insults and spinal cord lesions (4)

Supra nuclear bladder paresis is mainly treated h parasympatholytic drugs (10) sacral nerve cks (9) or sacral rhizotomy (8) with improvement 50 to 75 per cent of the patients However the atment of this bladder disturbance is mostly pallia

Only in a few cases is causal treatment of the mary neurolgoical lesion possible This report ers such a case

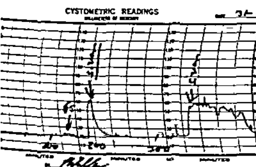
CASE REPORT

In 1975 a 56 years old woman with recurrent urinary incon tinence was referred for urodynamic investigation and treat ment She had suffered from urinary incontinence since 1960 In 1961 1962 1967 and 1972 she was treated by means of vaginal repair operations resulting in only a few months of continence

Careful history taking revealed that the urinary symptoms were mostly frequency urgency urge incontinence and nocturia 4 times Medium fill water cystometry reveal ed detrusor hyperreflexia (Fig 1) Urodynamic examination with simultaneous pressure flow EMG recording during voiding was normal Micturition-cysto-urethrography was normal and no objective stress incontinence could be dem onstrated

Treatment was started with parasympatholytic drugs with only minimal effect (Fig 2) Sacral nerve blockade was inef fective (Fig 3) Careful neurological examination revealed symptoms of cervical spinal cord compression but no peripheral paresis Myelography showed prolapsed cervical discs ($C_{V\ VI}$ $C_{VI\ VII}$) (Fig 4) The patient was treated with anterior cervical spondylodesis a m Cloward (5) in Nov ember 1975

The urinary symptoms gradually decreased postopera tively and cystometry 18 months later was normal (Fig 5) At three year follow up (November 1978) she had neither frequency urgency nor urinary incontinence only noc turia at times The patient was cured



g 1 31 I 1975 Cystometry before treatment showing trusor hyperreflexia (FS = first sensation siven = ne loss)

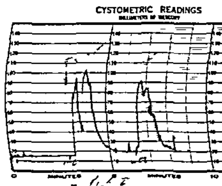


Fig 2 28 V 1975 Cystometry after 4 months treatment with parasympatolytic drugs (methantheline bromide (Banthine[R])) 50 mg q i d Detrusor hyperreflexia

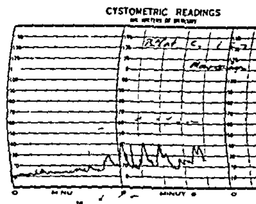


Fig 3 28 V 1975 Cystometry after bilateral blockade of S_{II} and S_{III} with bupivacaine (Marcaine[R]) Detrusor hyperreflexia

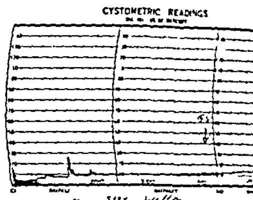


Fig 5 9 V 1977 Cystometry 18 months after a. tenor: dylodesis vertebrae cervicalis a m Cloward Noraxl tometry

CONCLUSION

Cystometry is the reflex hammer of the urologist and all patients referred with bladder disturbances to gynecologist neurologist or urologist should be studied using cystometry (11) If cystometry reveals signs of neurogenic bladder supranuclear or infranuclear paresis (6) a careful neurological history and examination must be undertaken If this investigation indicates central or peripheral neurogenic lesions further neuro-urological investigation must be performed with close collaboration between the neurologist and urologist (2)

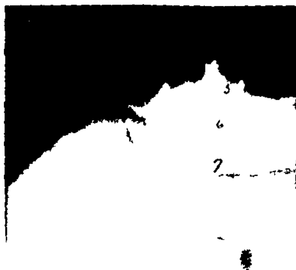


Fig 4 Cervical myelography showing prolapsed cervical intervertebral disc (C_{VI}-C_{VII})

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CASE REPORT

MÜLLERIAN MALFORMATIONS AND SIMULTANEOUS PREGNANCIES IN DIDELPHYS UTERI

Review and report of a case

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:r Congenital anomalies originating in the müllerian :e among the causes of gynecological and obstetrical ances that are commonly overlooked These cases he rate of 1 1 – 3 5 per cent in hysterographic ex ons

: authors have stressed the need to keep this type of n mind and to try to diagnose these conditions cor :specially when the patients are examined for trivial ints in the non pregnant state as well as during the .l period or after delivery

:ase presented is a multiparous Beduin woman with neous pregnancies in both cavities of an unexpected ys uteri The first twin female 2 000 gram was born : and the second female 2 250 gram by cesarean sec ollowing unsuccessful attempts at vaginal delivery cision to undertake surgery was taken for common ical reasons like inertia uteri and high presentation early diagnosis should result in adequate manage nd the earlier end of labor

; didelphys in the living adult was first mention 873 when Frankel cited the cases of Oliver and t as the only two recorded cases (1) Pfan el was the first to make a definite contribution ; direction when in 1894 he tabulated 12 cases rus didelphys in adults Miller (1) presented 5 (54 of the literature and one of his own) Only cases presenting two distinct fundi each with n cervix were considered when collecting these Stolper found 10 in 7 400 married women :bauer found 3 cases in 19 000 examinations (2) (3) established 1 case in 1 458 – 7 040 pregnan out 1 in 27 703 – 28 389 women and only one of twins Berkeley *et al* (Tortora) (4) consider a twin pregnancy is slightly more than seven commoner in the double uterus than in the nor

CASE REPORT

A 30-year-old Beduin woman para 6 two newborns with low birthweight died after delivery At the time she was delivered at home of a female fetus birthweight being 2 000 gram and the placenta was expulsed a few minutes after ad mission to hospital Abdominal examination revealed a se cond live fetus high head presentation mild uterine con tractions cervical dilatation of 1 5 cm X ray blood and urine tests revealed no abnormality Amniotomy was per formed but no progress was noted The next day a pitocin drip was attempted and 20 hours after the first delivery a cesarean section was performed Surprisingly two uteri were found the fetus being in the left one The size of the left uterus was adequate to a term pregnancy and the right uterus of a size adequate for a four month s pregnancy Each uterus had one tube and one round ligament on the ex ternal surface The peritoneal fold between the two uteri was easily visible A segmental transverse incision in the left uterus was made and a female normal fetus was born birth weight being 2 250 gram The placenta was normal Four months after delivery a hysterography was performed and two uteri with two cervices were seen Intravenous pyelography revealed no abnormalities

COMMENT

The term didelphys is derived from two greek words meaning double uterus More accurately the condi tion consists of two distinct and complete halves rather than a true reduplication of a normal uterus so that each uterus has only one set of ligaments and appendages arising from each lateral border Usual ly the term double uterus is applied to any condi tion resulting from the failure of complete fusion of the müllerian ducts (5)

The incidence found by different authors varies from 1 321 to 1 625 deliveries We found 29 anoma lies in 23 085 deliveries including 4 cases of double uterus or 1 796



Fig 1 Didelphys uteri after cesarean section in the left side

Different classifications have been suggested by different authors Classified according to müllerian origin Semmens (6) presents two groups

Group I functional uteri of single müllerian origin Bicornis bicollis unicornis bicornis unicollis

Group II functional uteri of dual müllerian origin Bicornis uterus subseptus arcuatus

Uterus didelphys is most likely to be found first during adolescence when the patient complains of some menstrual disturbance secondly at the time of premarital examination thirdly after marriage when the patient complains of dyspareunia or unexplained abortion and last during pregnancy

Hematometra is commonly associated with a double uterus (2) as are abortions Unusual fertility is demonstrated in many cases Fetal wastage is estimated between 23 per cent and 33 per cent (2 6) There is a great liability to premature labor (3) and labor is prolonged as a result of poor muscular development of the uterus a small rigid cervix and the encroaching non pregnant uterus (2) The incidence of breech presentations rises to 20 per cent in malformed uterus in transverse lie to 5 2 per cent in retained placenta to 15 per cent Maternal mortality is comparatively high and there is a higher rate of fetal and newborn mortality (3)

The duplexity of the uterus presents numerous instances of what may well be assumed to be examples of superfetation A case of twin pregnancy is reported by Dubierre where the interval between deliveries was 14 weeks Kustner finds a maximum interval of 74 days [both cited by (2)]

Physical signs observed at routine prenatal examinations that should arouse suspicion of congenital uterine anomalies are fetal limb flanking with over lie breech flanking with contralateral limb fa[illegible] fetal limb flanking with fundal notching [illegible] tion in the uterus positive Piscachek s sign [illegible] pregnancy and axial deviation of the uter[illegible] have stressed notching and broadening of the [illegible] fundus a floating head at term in a primigr[illegible] the absence of accepted causes of dispropor[illegible] well as abnormal lie recurring breech prese[illegible] trapped or retained placenta and a prolonged stage of labor All these constitute indica[illegible] post partum hysterographic evaluation which confirmation of the anomaly in almost 100 pe[illegible] of the cases accordingly to Hoy [cited by Sem[illegible] (6)]

If manual removal of the placenta become[illegible] sary obstetricians should be aware of the ph[illegible] non of triangular spasm and cornual poc[illegible] which are accentuated by the use of oxyto[illegible] non pregnant women probing of the uterus [illegible] uterine sound will often confirm the presen[illegible] septum (8) During dilatation and curettag[illegible] obligatory to assess the continuity of the uter[illegible] dus from one horn to the other with a blunt [illegible] ment so that the presence of any complete or [illegible] septum may be noted Hysterographically co[illegible] ly malformed uteri show rather rounded and [illegible] like horns whereas normal uteri have rela[illegible] horns (8) In the 56 cases of Semmens (6) [illegible] travenous pyelograms were done and 25 p[illegible] showed agenesis of one kidney and 8 per cen[illegible] kidney anomalies A possible genetic factor [illegible] etiology of uterine malformations has been p[illegible] by Polishuk (9)

Fig 2 Hysterography four months after the las[illegible]

ıhe management of labor in cases with uterine 'ormaties is controversial Findley (2) writes that treatment should not differ at all from that in the ly constituted uterus Hoffman (7) prefers an ve cesarean section Inertia uteri should be naged by abdominal delivery rather than oxytocin stimulating effect of which would cause horn ng abnormal fundal contraction patterns and cental separation (6) A vaginal septum should be as soon as it is recognized preferably in the ravid state (6)

although in our case it cannot be proved con sively that the first twin was delivered of the right rus signs like the size of the right uterus that have seen druing the intervention the unusual expul n of the first placenta before the delivery of the se d twin and the physiological cervical opening of eft uterus allow us to assume that both pregnan were simultaneous in the right and left uteri

The case was managed without a previous diagnos f double uterus Surgical intervention is indicated obstetrical common reasons like inertia uteri and n presentation However the thought of the of a uterine malformation even in a tiparous woman should surely prevent a delay in gnosis and adequate management

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CASE REPORT

EARLY DIAGNOSTIC SIGNS IN THE DEVELOPMENT OF A FALLOPIAN TUBF CARCINOMA

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tract A woman is presented in whom cellular atypia signs of abnormal fibrinolysis in a jet washing caused istent suspicion of malignancy after a benign curettage rly 3 years later a fallopian tube carcinoma was diagnos The value of determination of biological markers of olasia in addition to the cytologic interpretation of ine fluid is emphasized

inoma of the fallopian tubes is extremely rare incidence is reported to be 0 38 per cent of all cologic malignancies In most cases the true nosis is unknown prior to operation and the ase is usually found in an advanced stage (1 3) ing 1958 1969 the incidence in Malmö (admit e area 280 000 inhabitants) was 1 2 per cent i e 7 out of 595 gynecological malignancies (2)

cases of malignant ovarian tumors Fibrin/ mogen Degradation Products FDP (8) are fre ntly found in high concentrations in ascitic fluid Thus in theory malignant endometrial tumors ld accordingly be accompanied by increased in uterine fluid In 1975 when testing the lee Jet Washer (4) we therefore began to deter FDP in Jet Wash samples in addition to the logical interpretations (5)

is is a case report of a patient in whom high entrations of FDP in uterine fluid caused suspi of malignancy nearly 3 years before a fallopian carcinoma was diagnosed

CASE HISTORY

year old woman with menopause at 50 years of age had eral gynecologic health check up in 1975 The clinical ination was normal but the vaginal smear revealed a atypia of glandular cells Because of this a Gravlee Jet and a curettage were performed The cytologic diag was atypia without signs of malignancy but further control was recommended The FDP were found to be ab normally increased The histologic diagnosis after curettage was postclimacteric endometrium without sign of atypia

The presence of FDP particularly in combination with the cytological atypia caused suspicion of malignancy and the patient underwent hysterosalpingography hysteroscopy and another curettage All these examinations were normal Gynecologic examination and further vaginal smears during the next 2 years were completely normal

In the beginning of 1978 the patient complained of urinary incontinence and a watery discharge was seen in the vagina She was referred for a complete urogynecologic in vestigation which did not reveal any abnormalities At a gynecologic examination under anesthesia however a tumor with a diameter of about 3 cm was palpated at the site of the right adnexa Curettage revealed postclimacteric en dometrium

Ultrasonographic examination confirmed the existence of an adnexal tumor and cytologic examination of the vaginal discharge revealed atypical glandular cells with the same morphology as described in 1975 Another hysterosalp ingography was performed and showed a tumor at the right side of the uterus with a probable connection to the right fallopian tube

Laparotomy was performed and revealed an enlarged right fallopian tube containing clear serous fluid The distal end of the tube was occluded by a 2 5 cm in diameter hard grey white tumor which was adherent to the right pelvic wall The ovaries as well as the uterus were of normal size and appearance Both the adnexa were removed together with the uterus The histopathological diagnosis was adeno carcinoma of the right fallopian tube

DISCUSSION

Most probably the fallopian tube carcinoma was already present in 1975 nearly 3 years before the tumor was clinically diagnosed

Despite extensive examinations the only patholog ical findings were the presence of cell atypia without suspicion of malignancy in a routine vaginal smear and in an endometrial Jet Wash High concentrations of FDP were also noted in the Jet Wash sample The significance of the latter was at that time uncertain

The results of all other conventional examinations were normal The cytologic atypia in the Jet Wash was interpreted as a probably false positive finding (*6*) and subsequent vaginal smears were normal

In the beginning of 1978 the patient complained of urinary incontinence which she first noted in a mild form as early as in 1976 The symptoms of carcinoma of the fallopian tubes are vague and in most cases so slight that the disease is highly advanced before the patient seeks care However one of the symptoms may be an abnormal watery discharge interpreted as urinary incontinence

Since 1975 we have found abnormally elevated (≥ 10 mg/l) concentrations of FDP in uterine fluid in 71 per cent of patients with endometrial malignancies (12 out of 17) and in 38 per cent of patients with ovarian malignancies (6 out of 16)

The value of the FDP test is limited because of a relatively large number of false positive results (approximately 10 per cent) and has been replaced by lactate dehydrogenase (LD) isoenzyme analyses in the diagnosis of endometrial malignancies (7)

A new chemical method for the analysis of a tumor activator of fibrinolysis has however recently been developed (11 12) Later tests have shown elevated concentrations of this tumor activator and of FDP as well as an abnormal LD-isoenzyme pattern in the uterine fluid collected from the present patient prior to operation

Therefore in view of this somewhat unusual case it seems justified to suggest that the addition of biochemical analysis to the cytological interpretation of uterine fluid could be of value in the early diagnosis of gynecologic malignancies

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CASE REPORT

PRIMARY CARCINOMA OF THE BARTHOLIN GLAND

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act A report of a patient with a Bartholin gland r is presented Although this desease is rare it should rn in mind when treating common Bartholin gland en nents Bartholin gland carcinomas are misdiagnosed nmon cysts or abscesses in half of the cases leading to lerable delay in diagnosis

m a review of the literature concerning this disease recommendations are made

ary malignant tumors of the Bartholin gland are Klob reported the first case in 1864 and 200 have subsequently been reported in the world ture The clinical appearance of these tumors be very similar to that of a common Bartholin which is illustrated by the following case report

CASE REPORT

atient is a 32 year old para 4 who consulted the out t clinic of the hospital after observation of a firm and imes tender mass in the region of the left Bartholin n The tumor had been present for 6 months but had reased in size appreciably during this period The on ptom she had experienced was some degree of dys ria There was *no history of previous inflammation of* artholin gland

examination there was a 2 × 2 cm firm moveable luctuating non tender nodule in the area of the Bar gland on the left side Overlying skin was intact The ite part of the vulva was normal as was the gyne cal examination finding otherwise No pathological s were found in the inguinal regions

finding was diagnosed as a left sided Bartholin cyst ation of the cyst was performed 5 weeks later The was adherent to the underlying muscle but could be ed out without difficulty The specimen measured 1 5 × 2 cm and was firm without cystic cavity on scopical examination

art from a moderate hematoma the postoperative e was normal Histological examination showed a low entiated carcinoma of the adeno-acanthoma type ibly not radically removed

Radical vulvectomy with skin transplantation (but not lymphadenectomy) was carried out three weeks after the first operation Histological examination showed no rem nant of cancer Control examinations over a 9 month period have not shown any signs of recurrence and the patient has had no complaints

DISCUSSION

This case fulfils the four criteria for diagnosis of a primary cancer of the Bartholin gland as established by Honan (1897)

1 correct anatomic position of the tumor
2 location of the tumor deep in the labium
3 overlying skin intact
4 presence of some elements of glandular epithelium

These criteria are very strict and have probably decreased the apparent incidence of cancer originat ing from the Bartholin gland (1) although this type of tumor accounts for 3–8 per cent of all vulvar cancers (2)

Because of a different clinical behavior cancer of the Bartholin gland should be distinguished from other vulvar carcinomas

The median patient age for the diagnosis of Bar tholin gland cancer is 53 years (3) which is nearly a decade earlier than that for common vulvar cancers

Histologically about 40 per cent of the malignant tumors in the Bartholin gland are squamous cell carcinomas 46 per cent adenocarcinomas 8 per cent adenoid cystic carcinomas and 6 per cent carcinomas melanomas or undifferentiated malignant tumors (1 4 5) Adenoacanthoma as reported here is in the literature generally described as being a mixture of squamous cell carcinoma and adenocarcinoma

The most common symptom reported by other authors is the subjective observation of a tumor in the vulva (4) and this was true in the present case The tumor may be painful and cause dyspareunia On ex

amination there is an enlargement of the Bartholin gland often hard and indurated but there may be a cystic degeneration In approximately half of the cases reported in the literature the initial clinical diagnosis is that of a benign cyst or inflammatory process This results in a delay of 3 months to several years in establishing the correct diagnosis (3) It is important to remember that uncomplicated inflammatory disease of the Bartholin gland is uncommon after 40 years of age and does not occur at all in the post menopausal years (6)

Chamlian (3) recommends biopsy in the following situations

1 if induration is noted during incision or marsupialization of Bartholin gland enlargement
2 if necrotic material is drained
3 if there is slow healing after drainage or marsupialization

Lürman (7) suggests that all Bartholin gland enlargements should be subject to biopsy

Because of the small number of patients reported in the literature no uniform mode of treatment has been accepted However most authors recommend surgical treatment The surgical procedure varies from local excision to extensive vulvectomy including dissection of the inguinal femoral external iliac common iliac hypogastric obturator lower aortic and vena caval nodes

Chamlian (3) states that it is wise to tailor treatment to the individual patient rather than to advocate a standard mode of therapy for all patients

Most authors recommend radical vulvectomy combined with a bilateral inguinal and femoral lymph node dissection (2 4 8) Trelford (2) emphasizes the importance of dissecting deeply down to the urogenital diaphragm Lymphadenectomy is generally not necessary in adenoid cystic carcinoma of the Bartholin gland since this type of carcinoma is less aggressive and rarely exhibits regional or distant metastases (5)

CONCLUSIONS

It is important to be aware of the existence of [illegible] nant Bartholin gland tumors in case of [illegible] of the Bartholin gland with characteristics [illegible] ed above All Bartholin gland cysts which are [illegible] should be examined histologically

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SERUM LACTIC ACID DEHYDROGENASE AND ISOENZYMES DURING PREGNANCY AND LABOR

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tract Total serum lactic acid dehydrogenase activity (H) and the levels of LDH isoenzymes were investigated 4 women during early pregnancy (8–16th week) in 28 nen during late pregnancy (29–37th week) in 73 at term –42nd week) and in 27 during labor (38–42nd week) I activity was found to be elevated in severe pre eclamp- and in chronic hypertensive women during pregnancy as as during normal and dysfunctional labor No change established in total serum LDH during normal pregnan

DH 1 was increased during late pregnancy and at term evere pre eclampsia and during normal labor it was eased LDH 2 was also decreased in severe pre eclamp- and during dysfunctional labor LDH 3 was decreased ng late pregnancy but increased in severe pre eclampsia hange was observed in LDH 4 during pregnancy or in r LDH 5 was increased in normal and dysfunctional

tic acid dehydrogenase (LDH) is an enzyme found issues working the anaerobic metabolism of ohydrates catalyzing pyruvate to lactate Lactic dehydrogenase is especially abundant in skeletal cle *where its activity is greater than in smooth* cle such as in the uterine muscle (22 23 37)

During normal pregnancy many enzymes are more active than in the non pregnant state Most reports on LDH activity during labor show an increase (1 3 8 11 13 15 17 18 21 26 27 28 38 39 40)

There are only a few investigations concerning en zymes in sera during dysfunctional labor Only Bril liantova *et al* (3) have studied LDH They found a decreased serum LDH activity during dysfunctional labor

The lactic dehydrogenase present in blood and tis sues is separable into five isoenzymes by electropho resis (LDH 1 LDH 2 LDH 3 LDH 4 and LDH 5) The relative proportions of the individual isoenzymes vary from tissue to tissue The pattern of change in the normal serum isoenzyme pattern characterizes the tissue source of increased serum enzyme activity Lac tic dehydrogenase is normally present inside the cell but is passed into the serum after destruction of the cell or due to increased permeability of the cell

This study was undertaken to establish the effect of pregnancy and labor especially dysfunctional labor on serum lactic dehydrogenase and LDH isoenzyme levels *The effects of pre-eclampsia and chronic hy* pertension were also investigated

ıle I *The patients investigated*

		Week of pregnancy			Age (years)		Parity	
ups of patients	No of patients	Mean	SD	Range	Mean	SD	Mean	Range
ı pregnant	16				42 6	7 3	1 9	0–6
ly pregnancy	14	11 0	1 5	8–16	30 6	8 5	3 6	1–7
pregnancy	22	33 3	3 1	29–37	26 6	6 3	1 6	1–3
ith severe pre eclampsia	6	33 2	2 6		28 0	4 1	1 3	1–2
term	60	40 2	1 1	38–42	28 4	5 8	1 7	1–5
ith mild pre-eclampsia	5	39 4	1 1		24 8	7 1	1 2	1–2
ith hypertension	8	39 3	1 0		30 4	7 1	2 1	1–3
mal labor	13	40 2	1 2		26 6	7 3	1 6	1–4
mary dysfunctional labor	10	40 4	1 1		27 3	7 5	1 2	1–3
ondary dysfunctional labor	4	39 5	1 9		23 5	1 9	1 0	0

Table II *Total LDH (I U)and LDH isoenzymes (per cent) in sera of non pregnant and pregn*

	LDH		LDH 1		LDH 2		LDH 3		LDH 4		LDH 5	
	Mean	S E	Mean	S E	Mean	S E	Mean	S E	Mean	S E	[illegible]	[illegible]
Non pregnant (16)	262 4	18 9	25 6	0 1	38 7	0 7	25 1	1 1	4 9	0 7	5 1	[illegible]
Early pregnancy (8-16 wk 14)	2 0 9	14 3	28 5	1 6	38 1	0 7	23 8	1 4	4 4	0 5	5 [illegible]	[illegible]
Late pregnancy (29-37 k n 2)	284 3	7 7	31 1[1]	1 0	39 9	0 6	20 7[1]	0 8	3 7	0 3	4 6	[illegible]
with severe pre eclampsia (6)	460 5[4]	50 2	26 5[3]	1 6	35 2[3]	1 7	24 6[3]	1 3	4 3	1 5	9 [illegible]	
At term (38-4 k n 60)	301 3	9 0	28 3	0 6	37 8	0 5	22 9	0 6	4 8	0 3	6	[illegible]
with mild pre-eclampsia (5)	263 0	19 1	27 6	2 0	35 9	1 4	24 3	1 9	4 9	1 2	7 3	
with hypertension (=8)	355 8[5]	12 6	25 1	1 5	35 9	1 9	24 7	1 6	5 [illegible]	0 7	9 1	

1 $p<0\ 05$ from non pregnant 3 $p<0\ 05$ from late pregnancy 5 $p<0\ 001$ from term
2 $p<0\ 001$ from non pregnant 4 $p<0\ 01$ from late pregnancy

MATERIAL

The material consisted of 142 pregnant women 14 of whom were in early pregnancy (8 – 16 gestation weeks) 28 in late pregnancy (29 – 37 gestation weeks) 73 at term (38 – 42 gestation weeks) and 27 in labor The classification of the material according to the course of pregnancy (normal/pre eclampsia/hypertension) and labor (normal/primary dysfunctional/secondary dysfunctional) the week of pregnancy age and parity is shown in Table I

The pregnancies were divided into pre-eclampsia and hypertension by the criteria recommended by the American Committee of Maternal Welfare (6) 16 non pregnant women served as controls They were healthy and were not using any hormonal contraception The labor was regarded as normal when no disturbance was observed in the rate of cervix dilatation When cervix dilatation was slow from the start of labor the labor was classified primary dysfunctional In secondary dysfunctional labor the delay of cervix dilatation appeared after a normal initiation of labor All the blood samples in the labor groups were taken during the dilatation phase of labor

METHODS

The determinations of serum lactic dehydrogenase and LDH isoenzyme levels were made from clotted venous blood Total lactic dehydrogenase (EC 1 1 1 27) activity was determined according to the Scandinavian recommendation (5) at +37 C using an OLLI 3 000 [illegible] chemical analyzer (Ollituote Oy Kivenlahti Fi[illegible] reagents made by AB Kabi (Sweden) Lactic dehydro[illegible] activity is expressed as units (I U) per litre of serum

The fractionation of LDH isoenzymes was perfor[illegible] cellulose acetate membrane (Beckman California U[illegible] Electrophoresis was carried out at 150 V for 40 m[illegible] after which the fractions were developed accor[illegible] method of Dade (Iso-Form LDH Merz & Dade A[illegible] Switzerland) on the membrane and scanned by a [illegible] Model 110 densitometer (California U S A) to [illegible] the percentage activity of each fraction

The statistical analyses were made with S[illegible] and $p<0\ 05$ was regarded as statistically sig[illegible]

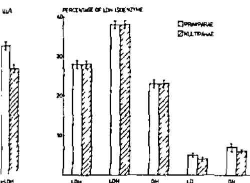
RESULTS

The results shown in Table II indicate th[illegible] pregnancy serum LDH 1 was increased ([illegible] and LDH 3 decreased ($p<0\ 05$) compare[illegible] non pregnant state At term serum LDH [illegible] *significantly* ($p<0\ 001$) increased No cha[illegible] observed in total serum LDH activity dur[illegible] cy either early or at the end of pregnancy

Table III *Total LDH (I U) and LDH isoenzymes (per cent) in sera of women with normal and dys[illegible] labor*

	LDH		LDH 1		LDH 2		LDH 3		LDH 4		LD[illegible]
	M	S E	Mean	S E	Mean	S E	Mean	S E	Mean	S E	M[illegible]
At term (60)	301 3	9 0	28 3	0 6	37 8	0 5	22 9	0 6	4 8	0 3	6 [illegible]
Normal labor (13)	405 [illegible][3]	27 1	24 8	1 0	35 7	1 3	24 2	1 3	5 4	0 5	[illegible]
Primary dysfuntional labor (10)	365 6	[illegible]1 7	[illegible]6 4	1 6	34 9	0 9	24 2	1 2	[illegible] 3	0 8	9
Secondary dysfunctional (4) labor	649 0[3]	675 4	27 2[4]	0 5	33 1[3]	0 5	[illegible]3 5	1 9	5 9	1 1	1 [illegible]

1 $p<0\ 05$ from term $p<0\ 01$ from term 3 $p<0\ 001$ from term 4 $p<0\ 05$ from normal labor 5 $p<0\ 01$ from normal labor
6 $p<0\ 01$ from primary dysfunctional labor



1 Total LDH and isoenzymes in sera of primiparae and ...iparae at term

...i patients with severe pre-eclampsia at 29 37 ...ks gestation total serum LDH was higher ... 0 01) than in healthy pregnant women at that ...od of pregnancy (Table II) The same applied to ...I 3 isoenzyme ($p<0\ 05$) The levels of LDH 1 ...LDH 2 were decreased ($p<0\ 05$) in severe pre ec...psia In mild pre eclampsia no changes were ob...d compared with the healthy pregnant women at ...ame gestation period (week 38-42) but in hyper...ve women total serum LDH was higher ... 0 001) than in healthy women during pregnancy ...le II)

...tal serum lactic dehydrogenase and LDH isoen... levels were investigated in 31 primiparaes and in ...ultiparaes at 38-42 weeks gestation Fig 1 shows ... total serum LDH was greater ($p<0\ 001$) in ...iparaes (329 9±12 2 I U /l) than in multiparaes ...0±11 0 I U /l) No differences were detected in ... DH isoenzyme levels

...ring normal labor serum total LDH was very ...ficantly ($p<0\ 001$ *increased as it was during* ...ndary dysfunctional labor ($p<0\ 001$) and signif...tly so ($p<0\ 01$) in primary dysfunctional labor ...pared with the same gestation period (week ...2) without labor (Table III)

...able III shows that the LDH isoenzyme pattern ... similar in primary and secondary dysfunctional ...r in contrast to the women at term LDH 2 was ...ficantly ($p<0\ 01$) decreased in primary dysfunc...al labor and very significantly ($p<0\ 001$) in ...ndary dysfunctional labor LDH 5 was increased ... primary ($p<0\ 05$) and secondary ($p<0\ 01$) ...unctional labor During normal labor LDH 1 was ...eased ($p<0\ 01$) and LDH 5 increased ($p<0\ 01$) ...ble III)

When the parturient groups were combined serum total LDH activity ($p<0\ 01$) and LDH 1 ($p<0\ 05$) increased more in secondary dysfunctional labor than in normal labor (Table III) In secondary dysfunctional labor the total LDH activity was augmented more ($p<0\ 01$) than in primary dysfunctional labor

DISCUSSION

The present investigation indicates that serum total LDH activity does not change during an uncomplicated pregnancy This is in accordance with some authors (2 4 13 16 18 19 20 21 24 29 35 36 38 40) while others report an increase of LDH activity in serum during pregnancy (7 11 14 27 32)

Electrophoresis differentiates the LDH isoenzymes by their speed of movement LDH 1 being the fastest and LDH 5 the slowest Tissues with high aerobic metabolism (cardiac muscle brain kidney and erythrocytes) are rich in the rapid type LDH isoenzymes 1 and 2 (H type) Skeletal muscle and liver have a preponderance of the slow type LDH isoenzymes 4 and 5 (M type) (31)

In the pregnant and non pregnant state the serum mostly contains the rapid kind of LDH isoenzymes the muscle type (M type) being present in only small amounts (12 41) Investigations into changes in the different LDH isoenzymes in serum during pregnancy do not agree Hawkins & Whyley (12) and Miotti *et al* (29) report an increase of LDH 1 during pregnancy in keeping with this study LDH 3 and LDH 4 were found to be increased by Meade & Rosalke (27 28) and LDH 4 by Pulkkinen & Willman (32) but a decrease of LDH 3 is reported by Miotti *et al* (29) LDH 3 was decreased during pregnancy in this study too The explanation for the increase of LDH 1 and *the decrease of LDH 3 in late pregnancy in this study* is not clear

In pre-eclampsia Kubli (19) and Sammour *et al* (34) found an increase in total serum LDH activity but no change is reported by some authors (4 12 20) In severe pre-eclampsia serum LDH activity was increased also in this study but neither total LDH nor LDH isoenzymes were changed in mild pre-eclampsia LDH 1 and LDH 2 were decreased in severe pre eclampsia as shown by Sammou *et al* (34)

A probable source of release of LDH into the circulation in severe pre eclampsia is the uterine muscle as LDH activity increases in the myometrium during pregnancy (10 22 25 33 37) The increased LDH 3 in severe pre-eclampsia is likely to originate from the

myometrium because Meade & Rosalki (28) show that LDH 3 and LDH 4 and Hawkins & Whyley (12) that LDH 2 LDH 3 and LDH 4 are the main LDH isoenzymes in the pregnant myometrium Placenta is suggested to be the origin of the increased serum LDH in pre eclampsia as LDH 4 and LDH 5 were increased in serum and in the placenta in severe pre eclampsia (34) LDH 4 and LDH 5 were not changed in pre eclampsia in this study

In chronic hypertensive women at term total LDH activity was higher than in healthy pregnant women as shown by Pulkkinen & Willman (32) Serum LDH activity was greater in primiparous than in multiparous women This disagrees with the study of Pulkkinen & Willman (32) who claim more serum LDH in women during the third or subsequent pregnancy than in women in their first pregnancy

The most prominent feature of the present study was a relatively marked increase in total LDH activity during labor Such an increase has been presented in many other studies (1 3 8 11 13 15 17 18 21 26 27 28 38 39 40)

Placenta is regarded as the origin of increased serum lactic dehydrogenase activity during labor (8 11 21 28 38) as is muscle work (17 26) The source of LDH during normal labor could be the uterine muscle as suggested by some authors (13 15 18 28 39) because LDH activity increases in the myometrium during pregnancy (10 22 25 33 37)

The increase of total serum LDH was greatest in secondary dysfunctional labor It presumably originates mainly from the uterine muscle as LDH activity in the myometrium is decreased is dysfunctional labor of this kind (25)

The muscle type (M type) LDH isoenzymes are known to be increased in serum during normal labor (12 39) The isoenzyme LDH 5 a muscle type LDH isoenzyme was increased during normal and dysfunctional labor in this study As muscle type LDH isoenzymes are more active than the heart type (H type) in the myometrium during pregnancy (9 10 33) it is possible that the former are released from the myometrium into serum during labor Skeletal muscle could also be the tissue from which LDH partly originates during labor as suggested by Unbehaun *et al* (39) Another possible source of the elevated LDH 5 during labor could be the amniotic fluid cells since these tend to show increasing LDH 5 as pregnancy progresses (30) and an increase of LDH 5 in amniotic fluid with increasing gestational age has been confirmed (29) LDH isoenzyme 2 was decreased in dysfunctional labor in this investigation which [illegible] with the study of Brilliantova *et al* (3) who [illegible] decrease of heart type (H type) LDH isoenzymes [illegible] dysfunctional labor

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SPONTANEOUS LABOR AND ELECTIVE INDUCTION—A PROSPECTIVE RANDOMIZED STUDY

II Bilirubin levels in the neonatal period

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tract The effect of induction of labor on the neonatal ubin levels was investigated in a prospective randomized ly Forty three infants born after elective induction with ocin using the Cardiff infusion system and 38 infants after spontaneous delivery were studied Several fac other than oxytocin administration which could influ the bilirubin levels such as gestational age placental sfusion and feeding routines did not differ between the groups There were no differences with regard to pH in ilical vein Apgar scores haemoglobin and erythrocyte me fractions or bilirubin levels neonatally Thus there no evidence of an association between induction of la with oxytocin and jaundice during the neonatal period

ral earlier studies have shown an increased fre ncy of jaundice in the neonatal period after in d labor with oxytocin (5 7 9 12) Other authors not found this increase (2 3 10 11 14) Most hese studies have been retrospective and factors as intrauterine asphyxia gestational age dose of ocin and the placental transfusion have as a rule been evaluated Some authors have claimed that aturity resulting from the induction and not ocin is the factor responsible for the increased ubin levels (4 6)

nce the relationship between induction of deliv with oxytocin and the development of hyperbili nemia remained unclear we decided to compare bilirubin levels in newborn infants in a random prospective study in spontaneous and induced r at full term

MATERIAL

patients the methods of selection and the methods of ction have been described in a previous paper (17) ty four infants 43 born after induced labor and 41 r spontaneous labor were originally included Three of infants in the spontaneous group were born after pro- ed pregnancies and were induced They were therefore uded from this study

METHODS

Immediately after the delivery the infants were placed on the delivery bed at the level of the vulva and were left there until the cord had been clamped A blood sample was drawn from the umbilical vein exactly 60 seconds after delivery and the cord was clamped After that 0 20 mg Methergine(R) was given intravenously to the mother The oxytocin infusion was stopped and the dose given recorded The cord blood was analyzed for pH hemoglobin (Hb) and hematocrit (Hct)

The infants were followed with daily capillary bilirubin measurements until decreasing levels were obtained All in fants were followed at least until day three and a maximal value was noted for all of them At 24 – 72 hours of age venous hemoglobin and hematocrit were estimated There were no cases of immunization involving the Rh or ABO systems All infants were delivered at full term A maturity assessment using external characteristics (8) was performed on day two on all infants A routine physical examination was performed on day one and on day five to six All infants were breast fed on demand Naked weight was recorded dai ly

The investigation was approved by the Ethical Committee of the University of Linköping

RESULTS

There were no differences in bilirubin levels Hb and Hct between infants of primiparae and multiparae or between the two obstetrical departments Therefore the results were pooled All infants were healthy at the two routine examinations One infant in the in duced group had a slight postnatal asphyxia Seven infants developed cephal hematomas five of these in the spontaneous group Birth weight lowest weight during the first week gestational age from the men strual history gestational age according to maturity assessment Apgar scores and pH in the umbilical vein are presented in Table I There were no statisti cally significant differences between the two groups for any of these parameters There were no differ ences between the two groups with respect to hemo- globin and hematocrit in the umbilical vein hemo-

Table I *Birth weight lowest weight during the first week gestational age gestational age accord ty assessment Apgar scores and pH in umbilical vein in induced and spontaneous labor (Mean SD*

	Induced labor	Spontaneous labor
Birth weight g	3 642±442	3 7_4±485
Lowest weight during the first week g	3 376±436	3 448±458
Gestational age days	280±1	285±4
Gestational age according to maturity assessment days	290±12	281±8
Apgar score 1 min	8 8±0 7	9 0±0 4
Apgar score 5 min	9 9±0 4	9 9±0 3
pH umbilical vein	7 35±0 07	7 33±0 07

(n=43) * (n=38)

globin and hematocrit day two bilirubin levels day 1−3 or maximal bilirubin level during the neonatal week (Table II) There was no difference regarding the day for starting weight gain In the induction group the mean oxytocin dose was 4 94 IU (0 5−11 IU) There was no relation between total oxytocin dose and maximal bilirubin level Seventeen infants (39 5 per cent) in the induction group and 19 (50 0 per cent) in the spontaneous group had bilirubin levels above 170 μmol/l A statistical analysis of all the results showed no relationship between maximal bilirubin level and uterine activity measured in Montevideo units fetal heart rate decelerations Apgar scores pH in the umbilical vein hemoglobin or hematocrit day two There was however a tendency for heavy babies (birth weight above 4 000 g) to have lower maximal bilirubin ($p < 0\ 05$) Further if the delivery time (from a cervical dilatation of 4 cm to delivery) was short (<150 minutes) there was a tendency that the maximal bilirubin level was higher ($p < 0\ 05$) see Table III

Table II *Hemoglobin (Hb) and hematocrit (Hct) in umbilical vein hemoglobin and hematocrit day 2 (Hb 2 Hct 2) bilirubin levels day 1−3 (Bil 1 Bil 2 Bil 3) and maximal bilirubin levels (Bil max) in induced and spontaneous labor (Mean±SD)*

	Induced labor	Spontaneous labor*
Hb g/l	152±14	155±14
Hct %	45 4±4 7	47 2±5 4
Hb 2 g/l	186±14	184±21
Hct 2 %	54 2±5 0	5_ 4±7 7
Bil 1 μmol/l	80 _3	88±30
Bil 2 μmol/l	1_0 36	1 8±43
Bil 3 μmol/l	145±56	156±50
Bil max μmol/l	156 61	157±70

(n 43) * (n 38)

DISCUSSION

A correlation between induction of labor w cin and neonatal jaundice was suggested by *al* (12) In most studies reporting an increased rubin level after induction the increase has been and probably without clinical significa studies have been prospective Factors such tional age obstetrical analgesia as well as feeding routines can influence the bilirub neonatally (5) In the present study there were ferences between the two grups with rega factors and no difference in bilirub n levels demonstrated between the groups An analys *total material showed however that birth* related to maximal bilirubin level duri g week Infants with a birth weight of more th g had a tendency to lower bilirubin levels

An additional factor whi h might bilirubin levels in some earlier studies uterine contractions following induction of thereby a possible increased frequency of In the present study in whi h the deliveries pervised by *intrauterine pressure measu* fetal heart rate recordings (FHR) we found ences in FHR-changes Apgar score or pH bilical vein at delivery between the groups were there any significant differences in tivity or duration of labor (17) Even the analysis of the whole group did not show a between maximal bilirubin levels and u a short labor (<150 minutes) was rela ed bilirubin levels

An increased frequency of neonatal jaund induction of labor might to some extent by increased placental transfusion Sa showed that the placental transfusion bilirubin levels at 72 hours of age among as well as among full term infants Factors

le III *Maximal bilirubin level during the first k in infants with birth weight below or above 00 g and infants born after long (above 150 minu or short (below 150 minutes) delivery in induced spontaneous labor (Mean)*

	No of infants	Maximal bilirubin level
h weight		
4 000 g	61	166 μmol/l
4 000 g	20	132 μmol/l
very time		
150 minutes	19	182 μmol/l
150 minutes	62	149 μmol/l

of clamping the umbilical cord the time of giv oxytocic agents postnatally or the position of the nts with regard to the uterus after delivery may uence the degree of placental transfusion and t be taken into consideration In the present study these factors were kept constant The time for nping the cord 60 seconds postnatally was en because by then most of the placental transfu has ceased (18) Oxytocic agents can increase ental transfusion and for this reason Meth ne(R) was given immediately after clamping the l Because the position of the infant at delivery in ion to the uterus also influences the placental sfusion (18) the infants were placed on the deliv ed at the level of the vaginal outlet At this level blood flow between placenta and infants is not uenced by gravity Venous hemoglobin and hema it on days two and three (24–72 hours) were en as simple indirect measurements of the size of fetoplacental transfusion Venous hematocrit is wn to be related to the total red cell blood volume thus the placental transfusion Erythrocyte vol is fairly constant between 24–72 hours of age found no changes in postnatal hemoglobin or natocrit suggesting that the placental transfusion t be the same in the two groups No differences in ling routines were found

hus in the present study most factors which can uence the bilirubin levels neonatally were equal in groups There were no differences in bilirubin lev on days 1 2 3 or in the maximal bilirubin levels ing the neonatal period Therefore the following clusion can be reached

nduction of labor with oxytocin within the criteria our study does not lead to increased neonatal bili in levels It is not likely that oxytocin *per se* increases the risk for neonatal jaundice The half life of oxytocin in blood at parturition is short about 4 min utes (13) and oxytocin is readily degraded by the kid neys and the liver (15) It seems therefore unlikely that the oxytocin given in significant amounts will enter the fetal circulation and interfere with the me tabolism of bilirubin In studies in which such a rela tion has been postulated the increased bilirubin level is more likely to be the result of an increased fre quency of preterm deliveries and postnatal asphyxia or an increased placental transfusion

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SKIN BLOOD FLOW IN NORMAL PREGNANCY MEASURED BY VENOUS OCCLUSION PLETHYSMOGRAPHY OF THE HAND

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ract Total hand blood flow was measured by venous usion plethysmography in 14 healthy primigravid wom Consecutive measurements were made from the 15th of pregnancy until term and after delivery *During* nancy the mean hand blood flow measured under stan resting conditions with the subjects supine increased ressively from 7 7 in early pregnancy to 28 9 ml/100 nin at term Simultaneously the peripheral vascular tance decreased from 19 3 to 3 3 PRU_{100} When ex ied at 6 – 16 weeks after delivery hand blood flow and pheral resistance were not yet returned to normal

rmation about the peripheral circulation in preg y is sparse Venous occlusion plethysmography is nvenient and reliable method for measuring d flow in a limb segment and has been utilized in y studies on hand forearm foot and leg of preg women With regard to forearm and leg blood the results are conflicting Most authors have d an increase in the resting forearm blood flow ng the course of pregnancy (7 10 15 17) while rs were *unable to confirm any change at all* (2 8) blood flow has been shown to be slightly increas 3 10) unchanged (2) or even decreased (14) as pared to non pregnant values Foot blood flow s to be moderately increased in late pregnancy

oncerning hand blood flow there is general agree t that a considerable rise occurs in late pregnancy n compared with non pregnant values (2 7 8) ever the authors used different plethysmograph ater temperatures which obviously influenced the nitude of blood flow increase As the vascular of the skin is very sensitive to changes in perature only a slight decrease in water tempera will cause a considerable vasoconstriction

i the non pregnant state changes in forearm blood y reflect to a large extent changes in muscular od flow (3 9) and this was assumed also to be the in *pregnant women* (15) *Spetz and Jansson* (17) de simultaneous measurements of total forearm blood flow by plethysmography and of forearm muscular blood flow with the ^{133}Xe clearance technique in non pregnant and pregnant women and found a progressive increase in total forearm blood flow during normal pregnancy while muscular blood flow remained unchanged In non pregnant subjects there was a good correlation between forearm blood flow measured by plethysmography and ^{133}Xe muscle clearance These findings seem to indicate that the main increase in forearm blood flow during pregnancy is due to a rise in skin blood flow and not in muscle blood flow

Changes in skin blood flow are obviously best studied by hand plethysmography since skin is the main part of the soft tissues of the hand According to Abramson and Ferris (1) skin constitutes one third of the hand volume muscle 16 per cent and bones and tendons the rest the blood flow of which can be neglected The present study was performed in order to investigate hand blood flow at resting conditions in a series of young healthy primigravidae using a constant plethysmographic water temperature of 34 C which has been shown to be the most reliable temperature at least in non pregnant subjects (5)

MATERIAL AND METHODS

A group of 14 healthy primigravidae were selected for investigation None had to be excluded because of complications of pregnancy They were all out patients at the antenatal clinic of the hospital Their mean age was 25 years with a range from 20 to 30 years The stage of pregnancy was calculated in complete weeks of gestation from the date of the last menstrual period At the first examination which was performed at 15 to 16 weeks of pregnancy each woman was informed about the completely harmless investigation procedure and they all willingly cooperated in the study Their deliveries subsequently took place between February and May 1976 at 38 to 41 weeks of pregnancy the mean being 40 weeks Five women were smokers and smoked between 5 and 20 cigarettes per day None had smoked within an hour before the examination

Table I Mean arterial pressure (MAP) heart rate (HR) hand blood flow (Q) and peripheral vas. resistance (PRU_{100}) in 14 pregnant women at different stages of pregnancy Number of examinations (n)

Month of pregnancy	IV	V	VI	VII	VIII	IX	X	Post partum
MAP mm Hg	83±3	83±2	79±3	84±2	87±1	89±2	89±2	80±2
HR beats/min	74±2	76±4	77±2	79±1	82±4	84±1	86±2	67±2
Q ml/100 ml/ min	7 7±2 0	8 2±2 1	13 8±2 4	20 6±2 5	24 1±4 6	24 5±2 1	28 9±2 3	11 0±1 2
PRU_{100}	19 3±4 9	15 3±2 7	7 1±1 2	4 6±0 5	4 6±1 2	4 0±0 3	3 3±0 3	8 7±1 1
n	9	10	9	10	6	14	15	14

The experimental conditions were carefully standardised All measurements were performed in the same laboratory with a room temperature of 22 C Before starting the investigation all the women rested comfortably in bed for about 30 minutes During the measurements the women were in the supine position but in late pregnancy they were slightly tilted to the side to avoid inferior vena cava hypotensive syndrome Arterial blood pressure was determined in the left arm using a conventional sphygmomanometer

Venous occlusion plethysmography was applied to the right hand which was enclosed in a loosely fitting rubber glove provided with a rubber diaphragm tightly applied to a metal plethysmograph The plethysmograph was filled with water maintained at 34 C (5) by a thermostat Hand blood flow was measured by recording the increase in hand volume caused by the arterial inflow during a given period of time when the venous out flow was obstructed by a 6 cm wide sphygmomanometer cuff placed at the wrist The occluding pressure was at least 10 mm Hg below the arterial diastolic pressure i e about 40 to 60 mm Hg in most instances On each occasion about ten consecutive measurements were made with intervals of one minute The mean of these measurements was calculated and taken as hand blood flow expressed in ml per 100 ml tissue per minute The pulse rate was calculated from the plethysmographic recordings The peripheral vascular resistance was calculated by dividing the mean arterial pressure (diastolic blood pressure plus one third of the pulse pressure) by the hand blood flow value and expressed in arbitrary peripheral resistance units (PRU_{100}) Altogether 87 examinations were made during pregnancy and post partum within a period from 6—16 weeks after delivery Each woman was examined on at least five separate occasions during the course of pregnancy

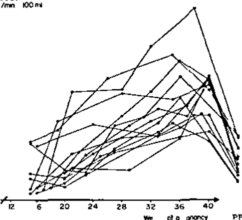
Mean±standard error of the mean (M±SEM) of blood pressure heart rate hand blood flow and PRU_{100} were calculated at different stages of pregnancy The results were statistically compared using a pairing design t test The difference was considered to be statistically significant when p was less than 0 02

RESULTS

Mean length of pregnancy at the time of delivery was 40±0 weeks Mean infant birth weight was 3 536±114 grams All were single births The results are summarised in Table I The mean arterial blood remained unchanged during the time period pregnancy studied even if a non significant rise 83±3 mm Hg at 15–16 weeks to 89±2 mm Hg 37–40 weeks could be noticed The post value 80±2 mm Hg was significantly lower than of the las 8 weeks of pregnancy The heart rate increased from 74±2 at 15–16 weeks to 86±2 beats minute at 37–40 weeks This difference cally significant Post partum the heart rate significantly lower compared to late but not pared to early pregnancy The main purpose heart rate recordings was to make sure that the subjects were in an acceptable resting state dur examinations

Hand blood flow increased continuousl the entire pregnancy taking into account a between individual women (Fig 1) The rise is obvious from Fig 2 where the mean graphically plotted against time There is a signi increase from 7 7±2 0 at 15–16 weeks to 28 9 37–40 weeks Mean hand blood flow post 11 0±1 2 ml/100 ml/min was significantly than in late pregnancy but still higher than at 1 weeks of pregnancy Hand blood flow of the women who were smokers did not differ from the non smokers Their blood flow values ly distributed within the values of the whole g

As expected peripheral vascular resistance d followed the changes in hand blood flow and s nificantly lower in late than in early pregnancy post partum value 8 7±1 1 PRU_{100} was signifi higher than that in late pregnancy but still low at 15–16 weeks Hence blood flow and vas resistance were not completely normal by weeks after delivery No correlation between birth weight and the magnitude of hand blood could be found



/ Individual hand blood flow values of 14 women in ion to length of gestation and at 6–16 weeks after ery (P P)

DISCUSSION

present study confirms the results of earlier in igations (2 8) Ginsburg and Duncan (8) found ncrease in hand blood flow from 2 7 ml/100 nin before 14 weeks to 18 1 ml near term The ent comparable figures are 7 7 ml at 15–16 ‹s and 28 9 ml/100 ml/min at 37–40 weeks of nancy The difference between the present results earlier findings may well be explained by the fact Ginsburg and Duncan (8) used a plethysmo- hic water temperature of 32 C and a room erature of 20 C while in the present study the esponding temperatures were 34 C and 22 C res ively Among other technical details the tempera factor is of significant importance when measur uch a sensitive parameter as hand blood flow On whole individual values must be assessed with t caution since the variability of the circulatory imeters is considerable between different series between subjects within the series The conclu that can be drawn from Ginsburg and Duncan ind the present series both studied under strictly dardised resting conditions is that the mean in se in hand blood flow can be estimated to be 20 ml/100 ml/min from early to late pregnancy he individual women there was an increase rang from 11 5 to 49 5 ml/100 ml/min as shown in the sent study

arlier observations (11) indicating that the mean rial pressure remains virtually unchanged during gnancy were also confirmed The pulse pressure seems to be a little higher during pregnancy mainly because of a decreased diastolic pressure The earlier reported increase in heart rate of about 15 beats per minute (11) was also observed in the present study These changes start early in pregnancy as does the early rise in cardiac out put (11)

The increased hand blood flow reflects mainly an increased skin blood flow This indicates a pro gressive vasodilatation in the skin during pregnancy which is an old observation Pregnant women feel warm are most comfortable in cold environment and their skin temperatures are high (6 10) The in crease in blood flow is most pronounced in the distal parts of the extremities because skin constitutes the principal part of hands and feet whereas in the forearm skeletal muscle constitutes the greater part Previous studies from this department (15 17) show ed however that the mean forearm blood flow in late pregnancy was 12 3 ml/100 ml/min at a plethys mographic temperature of 36 C 9 0 ml at 34 C and 6 9 ml at 26 C This is still a considerable rise over the non pregnant mean of 2 5 ml/100 ml/min at 34 C The blood flow increase within the skin com partment of the legs is probably very small if any (2 8 10 14) It has not been possible to measure skin blood flow in other regions of the body with presently available methods

Ashton (4) found recently that smokers in the last trimester of pregnancy had higher foot blood flow and toe and finger temperature than non smokers He suggested that the rise in skin blood flow believed to occur in pregnancy applied mainly to smokers This surprising suggestion is not supported by the present study where hand blood flow was equally high in smokers and non smokers in the second half of pregnancy

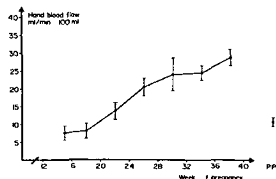


Fig 2 Mean hand blood flow (M±SEM) at different stages of pregnancy and at 6–16 weeks after delivery (P P)

The reason for the vasodilatation in the skin is obscure Estrogens have been demonstrated to produce peripheral vasodilatation in sheep (18) but no changes in hand or forearm blood flow were observed when naturally occurring estrogens were given by infusion into the brachial artery of non pregnant subjects (13) On the other hand the vascular bed in pregnant women may react differently to hormonal stimuli compared to that in non pregnant women The fact that hand blood flow was still elevated in the post partum period in the present as well as in Ginsburg and Duncan s (8) study does not support the concept that placental hormones are responsible for the vasodilatation in the vascular bed of the skin A more probable explanation is the presence of decreased tone of the vascular smooth muscle due to a decreased sympathetic activity and/or to a decreased sensitivity to vasoconstrictor agents No conclusions can be drawn from the present study with regard to structural changes of the vascular bed since for practical reasons it was not possible to achieve maximal vasodilatation

The physiological purpose of an increased skin blood flow may be to dispose of the increased energy produced by maternal and fetal sources during pregnancy From this point of view it would seem reasonable that skin blood flow should be greater if the fetus was large and thus produced more energy There was however no correlation between fetal weight and hand blood flow

Previous studies (12 16) have shown a reduced peripheral blood flow in pregnancies complicated by toxaemia and it has been suggested that this peripheral vasoconstriction takes place mainly in the skin (12) The relation between toxaemia and peripheral circulation is incompletely understood The present study of skin blood flow in the hand is aimed to serve as a basis for further studies in pregnancies complicated by hypertension

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SERUM LEVELS OF HUMAN PLACENTAL LACTOGEN DURING AND AFTER PRENATAL DEXAMETHASONE THERAPY

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act Thirteen pregnant women were treated with 4 mg iethasone intramuscularly three times daily for seven during the last trimester of pregnancy in order to pre he respiratory distress syndrome (RDS) in the neonate mination of human placental lactogen (HPL) was daily during the treatment and at intervals of 2–3 afterwards No changes in HPL were seen during the ient One week after the treatment had been stopped istically significant decrease in HPL was observed 01) The levels returned to normal during the follow eek It is presumed that the observed decrease in HPL be regarded as a result of a direct depression of placen nction caused by the dexamethasone therapy

implications of this finding for the fetus are not but in cases of placental insufficiency glucocorticoid nent should not be employed

ohylactic treatment of pregnant women with ptoms of threatened premature birth using high s of glucocorticoids has become increasingly mon after Liggins and Howie (12) demonstrated this treatment is able to reduce the incidence of ratory distress syndrome (RDS) in premature in i The dosage of glucocorticoid (betamethasone) loyed by Liggins and Howie (12) was empiric it is still not clear exactly what dosage of cor teroid should be employed or for how long in r to obtain an optimal effect with regard to the ention of RDS

ry little is known of the risks to the unborn in involved in the treatment in particular possible term risks have recently been the subject of ate (1 7)

he treatment brings about a considerable suppres of both the serum levels of estriol and the excre of estriol in the urine (3 18) Thus this parameter ild not be employed for evaluating the condition he feto-placental unit as long as the treatment is rogress neither may it be used in the period im liately following discontinuation of the therapy It been shown that no change takes place in the m levels of human placental lactogen (HPL) dur the treatment of pregnant women with beta methasone (13) or with dexamethasone (26) For this reason it has been suggested that HPL levels are a reliable parameter during glucocorticoid treatment

In the present investigation the serum levels of maternal HPL have been followed during and after treatment with dexamethasone in consecutive cases where birth did not occur in connection with the treatment

MATERIAL AND METHODS

During a 1 year period 32 patients were admitted to the Department of Obstetrics and Gynecology of the Kolding Hospital in the last trimester of pregnancy with symptoms of threatened premature birth Indications for the com mencement of treatment with 4 mg dexamethasone intra muscularly 3 times daily for a maximum of 7 days were present in all of these patients Thirteen of them did not give birth in connection with the treatment and comprise the pa tient material

Three of the pregnancies were twin pregnancies Four of the patients had at that time been subjected to cerclage of the cervix Apart from these factors the pregnancies were uncomplicated in particular none of the patients suffered from hypertension or symptoms of toxemia of pregnancy None of them were disposed to diabetes mellitus or had signs of intrauterine growth retardation

All of the patients were kept in bed and all but one were in accordance with the regime of the department put on the following additional treatment phenobarbital orally in doses not exceeding 100 mg daily and opium suppositories of 50 mg 3 times per day Five of the patients were also given progesterone suppositories of 500 mg 3 times per day Only one of the patients in this material received beta mimetic drugs The additional treatment was commenced at almost the same time as the dexamethasone treatment and was not changed during or in the week following the dexa methasone treatment

On the day before and each morning of the treatment a blood sample was withdrawn for the determination of HPL levels Blood samples were also withdrawn at intervals of 2–3 days during the two weeks following the discontinua tion of the dexamethasone treatment

Serum levels of HPL were determined by radioimmuno-assay (The Radiochemical Centre HPL Immunoassay Kit(R) Amersham)

The two-way analysis of variance was employed in the statistical analyses of the results

Table I *Individual and mean HPL levels in 13 patients before during and one and two week, with dexamethasone 12 mg per day for 7 days*

Patient	Weeks of gestation	Serum levels of HPL mg/l Before	1 week	2 weeks	3 weeks
1	34	7 3	7 2	6 3	6 2
2	34	4 7	5 4	5 4	4 9
3	31	12 8	13 6	8 7	15 0
4	30	5 7	5 5	5 1	6 8
5	32	7 2	6 4	6 0	6 4
6	34	9 0	8 0	7 4	8 1
7	30	6 6	6 8	5 8	7 0
8	31	6 8	7 2	6 3	8 5
9	32	9 2	9 4	8 9	9 8
10	32	8 4	9 1	7 8	10 1
11	33	3 4	3 1	2 8	3 7
12	34	8 2	7 6	7 0	7 7
13	29	4 8	4 9	3 7	4 9
	Mean	7 24	7 25	6 25	7 62
	SD	2 42	2 57	1 78	2 90
	P		ns	<0 01	ns

twin pregnancy

RESULTS

The results of the determination of the serum levels of HPL obtained before and during treatment with dexamethasone showed almost no variation and no significant changes were demonstrated The values obtained immediately prior to and at the end of the dexamethasone treatment are shown in Table I One week after the discontinuation of treatment there was a statistically significant fall in the HPL levels ($p<0\ 01$) however after a further week these had risen to a level above the initial values but this increase was not statistically significant The rise corresponded to that expected as a result of the increase in gestational age

All the patients later gave birth to healthy infants no signs were present in either mothers or infants which could be interpreted as indicating side effects or complications to the dexamethasone therapy

DISCUSSION

The synthesis of HPL takes place in the syncytiotrophoblast layer of the placental epithelium (16) and several investigations have shown that there is a significant positive correlation between maternal serum levels of HPL and the weight of the placenta (10 15 17) According to Samaan *et al* (14) and Spona and Janisch (21) the synthesis of HPL is autonomous and it has been demonstrated synthesis is unaffected by factors such as posture (25) or circadian variation (6 22) A of studies suggest that metabolic mother affect the synthesis of HPL Thus hypoglycemia bring about a rise in HPL levels hyperglycemia causes a fall (5 8 19 24) or diabetic women in the third trimester of other investigators have been unable to changes in HPL levels corresponding to blood glucose when the latter are brought oral glucose tolerance tests (6 9)

It appears to be well documented that measurements of HPL are a good indicator functional condition of the placenta (10 11 would therefore be reasonable to presume the in HPL levels is an expression of a reduct cental function and that this other things equal will increase the risk of fetal distress

The levels of HPL were unchanged during treatment in the present investigation this is in ment with earlier studies (13 26) However a st cally significant fall in HPL levels was demonst during the week following the discontinuation treatment but this was a transitory phenomen asmuch as normal values were again observed week later

The treatment of non pregnant women with corticoids causes a displacement of the metab

ards gluconeogenesis According to Tuimala et al this effect appears to be less pronounced in gnant women than in normal subjects during dex treatment Thus they found no changes lood glucose but a rise in serum free fatty acid ls and serum insulin levels As these changes are ely related to the steroid treatment they cannot ain the changes in HPL levels found in the pre investigation

fall in HPL levels also appears to be unrelated to nges in serum levels of estriol as these occur dur glucocorticoid treatment

examethasone treatment in the present study was n for a period of 7 days Theoretically there is the ibility that treatment with dexamethasone for a long period would bring the patient into a state lative suprarenal gland insufficiency with subse nt changes in the metabolic status However ld this be correct it would be more reasonable to ct a compensatory rise in HPL levels rather than decline demonstrated in the present investigation ntil this question has been studied further one assume that dexamethasone treatment of our ts has had a direct inhibitory effect on placental on

slight fall in serum levels of HPL as demon l here will presumably be of no clinical impor in the majority of cases but in patients where tal function is already affected dexamethasone ent may cause a further reduction with a uent risk to the fetus This might be a possible ation of the relatively higher mortality follow xamethasone treatment both antenatally and tally found by Liggins and Howie (12) in the complicated by symptoms of severe toxemia of ancy

chose the present treatment with dexametha because of the good results obtained by Caspi et However we consider it necessary to point out ossible danger of extending the treatment with high doses of glucocorticoid to so many days reatment should only be commenced on strict tions and where possible first after evaluation e L/S ratio Conditions that influence the ntal function should be considered to be con dications to antepartum glucocorticoid therapy

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FETAL SYSTOLIC TIME INTERVALS AFTER PARACERVICAL BLOCK DURING LABOR

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ract Fetal systolic time intervals (FSTI) were recorded / 10th second (s) during uterine contractions in 25 par 'nts in the first stage of labor before and after paracer block (PCB) Twentytwo patients had good or excel 'elief of pain The newborn infants were not depressed ter PCB the duration of the R – R and $S_1 - S_2$ intervals ased A close correlation was found between the R – R $S_1 - S_2$ intervals both before and after PCB and dur arly decelerations recorded before and after PCB The S_2 interval was prolonged after PCB even after correc for the heart rate

e $R - S_1$ interval and the amplitude of the first part of irst heart sound (S_1) also increased after PCB

e FSTI showed a conspicuous cyclic variation during ne contraction The S_1 amplitude decreased after the of contraction the others increased simultaneously

e results contradict the assertion that PCB causes fetal xia or reduction of the maternal placental circulation 'entralization of the fetal circulation possibly combin th a direct effect of local anesthetic on the fetal heart d explain the changes found after PCB

e cyclic variation of the parameters during uterine action is probably caused by a transfer of blood be 1 the placenta and fetus The changes of myometrial mics after PCB as shown by the alteration of the "s of the amniotic pressure curve are compatible with ransfer of blood

ne effects of local anesthetics on the mechanical ole of the fetal heart have not been studied in il in vivo Active systolic pressure and contractili P/dt) of the left ventricle is decreased by mepiva e in the isolated human heart from midpregnancy and atrioventricular and intraventricular conduc is delayed Decreased contractility prolongs T and the $Q - S_2$ interval in the adult human (8) he present investigation was undertaken to study effect of PCB on fetal cardiac performance dur labor

METHODS

PCB was given as described before (11 1) using bupivacaine with adrenaline (Marcain-Adrenalin[R] Bofors) 40 mg – 40 µg fluid volume 16 ml divided into 4 doses Care was taken to place the local anesthetic solution as superficially as possible at points where the patient felt puncture pain which she could locate to he correct sid of her body Minimal axial force was applied to the Kobak needle to avoid distortion of the lateral vaginal fornices The supine hypotensive syndrome was avoided

The fetal electrocardiogram (FECG) was recorded with a scalp electrode and the fetal phonocardiogram (FPCG) from the maternal abdomen as earlier described (13) The amniotic pressure was recorded with an open ended catheter (11) and the phases of the amniotic pressure curve were calculated as described previously (12) The peak pressure of uterine contractions was designated active pressure (AP) AP = total pressure minus resting pressure (11) and the time when AP occurred time of active pressure (t_{AP}) T_{AP} was chosen as zero time The parameters were read every 10 seconds (s) with the first reading point 40 s before t_{AP} and the last 40 s after t_{AP} Deviations up to 3 s from a reading point were allowed to avoid FPCG disturbance Each plot was the mean of 3 – 5 individual readings

From the FECG curve the duration of the cardiac cycle (R – R interval) PR time and RS wave duration were measured *The fetal electrical axis was calculated (20)* according to the principle of Larks (15) From the FPCG curve the duration of mechanical systole ($S_1 - S_2$ interval) and the first and second heart sounds (S_1 and S_2) were measured Correct timing of the start of S_1 was controlled by counting the number of deflections of S_1 The amplitude of the two parts of S_1 recognized (S_1 and S_{1b}) and the two parts of S_2 (A_2 and P_2) were measured to the nearest 0 5 mm

The $R - S_1$ interval was measured as the time from the crossing of the first limb of the R wave with the FECG base line to the crossing of the first high frequency deflection of S_1 with the FPCG base line The $R - S_1$ interval was use instead of the $Q - S_1$ interval due ot variation of the Q wave It represents the electromechanical lag period and a part of the isovolumetric ventricular contraction (8) Time intervals were measured to the nearest 2 5 millisecond (ms) the paper speed was 100 mm/s

Patients PCB was offered to patients who obviously suf

Table I *Clinical features of patients and their newborns*

	No of patients
Nulliparae	18
Multiparae	7
Admitted for	
early labor	13
ruptured membranes spontaneous start of labor within 24 hours	6
induction	6
Infusion of oxytocin	
for induction	*6*
for stimulation	3
Miscolored amniotic fluid before PCB	3

	Mean	Range
Maternal age years	24 8	18 – 31
Duration of pregnancy days from LMP	284	274 – 303
Friedman index after PCB cm/hour	5 1	0 8 – 12
Weight of newborn infant g	3 769	2 960 – 490
Apgar score 1 min of age*	8 4	4 – 9
Apgar score 5 min of age	9 1	4 – 10
Weight of placenta g	691	400 – 1 100
Length of umbilical cord cm	*54 2*	*32 – 83*

*One newborn infant got Apgar 4 points at 1 and 5 min of age (occiput posterior position secondary arrest of labor newborn infants got Apgar 6 points at 1 min of age (Pethidine given to the mothers after PCB) The later course of all newborn infants complicated

fered from the pain of labor and had only received small doses of N_2O 50 per cent in O_2 The FPCG recording should be distinct with minimal noise Twentynine parturients with a single fetus without mechanical disproportion and with the fetal head engaged in the pelvis were included

Four cases were excluded due to disturbance of the FPCG curve especially before PCB The readable parts of the curves showed no significant deviations from the means of the remainders

Statistics By comparing all the values before PCB (n = 225) with all the values after PCB the standard error of the difference was calculated for each parameter At each reading point (n = 25) the significance of the differences were evaluated by the Wilcoxon s signed rank test for paired differences the two tailed test as some results were not normally distributed Correlation were calculated on a desk computer and the statistical significance was calculated as described by Armitage (3)

RESULTS

Table I shows clinical details Twelve patients got complete relief of pain and were unable to report contractions 5 of them fell asleep Ten cases had a good effect but they could feel some discomfort or pressure In 3 parturients the PCB was less effective another dose PCB or pethidine being necessary 45 to 60 minutes after the first Seven patients had pronounced subjective and objective evidence of hyperventilation (paresthesia numbness presence of Chvostek's sign or carpal spasm) which disappeared a few minutes after PCB Acid base studies were not performed Maternal blood pressure did not change significantly during the experiment

The PR time did not change during uterine contractions *the mean duration before PCB was 102 5* ms (range 85 – 120 ms) and after PCB 100 (range 85 – 120 ms) The QRS axis showed a viation to the left at t_{AP} both before and after Between contractions the mean axis was + (range 113° – 177°) before PCB and + 141 120 – 174°) after it The RS wave duratio FECG was not influenced by uterin contra PCB

*R – R Interval The mean duration of the R-*val before PCB (n = 225) was 442 4 ms (minute) and after PCB 457 2 ms (131 beat The difference is statistically significant (P Disregarding short time variation and changes greater than 20 ms between con fetuses had an increased R – R interval shorter R – R interval after PCB

Table II shows the mean values at each point After PCB the R – R interval was sign prolonged only after t_{AP} giving its mean biphasic or cyclic course

$S_1 - S_2$ Interval The $S_1 - S_2$ interval 3 7 per cent from a mean of 194 1 ms before 201 3 ms afterwards ($p < 0\ 0005$)

Comparing each reading point before an PCB (Table II) the differences are significant tically except 10 and 20 s before t_{AP}

The duration of the R – R and $S_1 - S_2$ in were closely correlated before PCB r $p < 0\ 0005$ after PCB $r = 0\ 65$ $p < 0\ 0005$ Th of regression of $S_1 - S_2$ on R – R before ($y = 0\ 25x + 83$) and after PCB ($y = 0\ 17x + 124$ in the observation range testing the differen tween the slopes (3) give $p > 0\ 3$

Correcting the $S_1 - S_2$ interval for heart

Table II Duration of the R−R S_1-S_2, S_1-S_{2c} and $R-S_1$ intervals at each reading point before and after PCB in milliseconds means and standard error of the means SE

		Reading points (seconds)								
		−40	−30	−20	−10	t_{AP}	+10	+20	+30	+40
Before PCB										
R−R	mean	442 9	438 2	444 1	443 2	447 7	445 7	442 0	434 5	443 4
	SE	8.2	8 3	6 3	5 1	10 6	8 5	5 7	5 4	6 1
S_1-S_2	mean	192 0	191 2	195 6	195 3	195 7	195 7	193 1	193 3	195 0
	SE	3 1	3 2	2 3	2 6	2 5	[illegible] 7	2 2	2 1	2 1
S_1-S_{2c}	mean	288 6	288 8	294 0	293 5	293 0	293 3	290 5	293 2	[illegible]93 1
	SE	3.2	3 0	2 3	3 5	2 4	2 3	2 4	2 3	2 6
$R-S_1$	mean	32 9	33 1	32 8	33 5	33 7	34 3	34 0	33.5	33 3
	SE	1 1	1 0	1 1	1 2	1 1	1 1	1 3	1 1	1 1
After PCB										
R−R	mean	449 9	443 6	436 5	452 9	471 9	469 6	463 3	466 4	460 7
	SE	7.5	6 9	5 8	7 4	11 1	11 2	10 7	10 2	9 4
S_1-S_2	mean	200 4[b]	197 3[a]	196 8	198 9	201 9[b]	202 9	[illegible]03 9	206 0	203 6
	SE	2 3	2 3	2 7	2 4	2 3	2 3	2 4	2 3	2 0
S_1-S_{2c}	mean	299 1[c]	296 4[b]	297 8	[illegible]95 8	294 7	296 8[a]	300 2[c]	301 4	300 6
	SE	2 5	2 5	3 0	2 4	2 9	3 0	2 5	3 0	2 8
$R-S_1$	mean	34 9	35 7	35 0[b]	35 6	37 0	37 5[b]	36 7	37 1	37.2
	SE	1 1	1 1	1 2	1 6	1 7	1 7	1 6	2 0	1 8

At each reading point the values before and after PCB are compared using Wilcoxon s signed rank test for paired differences, no symbol p>0 05 $^{a}p<0.05$ $^{b}p<0.0?$ $^{c}p<0.01$

$S_1-S_{2c}=\frac{S_1-S_1}{\sqrt{R-R}}$ where the R−R interval is given in seconds (2)

S_{2c}) by the use of Bazett s formula (4)

$$S_1-S_{2c}=\frac{S_1-S_2}{\sqrt{R-R}} \qquad (2)$$

mechanical systole was still longer after PCB than before it (Table II) The S_1-S_2 and S_1-S_{2c} intervals showed cyclic variation during uterine contrac

case got early decelerations (9) starting 20 min after PCB and persisting until delivery (Fig 1) a close correlation between the R−R and S_1-S_2 intervals $r=0\ 81$ $p<0\ 001$

Another case had early decelerations both before and after PCB Correlating the S_1-S interval with the R−R interval before PCB gave $r=0\ 89$ $p<0.001$ $y=0\ 15x + 123$ $n=29$ and after PCB $r=0.90$ $p<0\ 001$ $y=0\ 15x + 125$ $n=29$

In one case a typical PCB bradycardia developed 6 minutes after PCB lasting about 7 minutes During the period of bradycardia the correlation between the R−R and S_1-S_2 intervals persisted and the S_1-S_{2c} interval remained unchanged

$R-S_1$ **interval** Recorded between contractions before PCB the $R-S_1$ interval correlated with the weight of the newborn $r=0\ 66$ $p<0\ 001$ It was 8 5 per cent longer after PCB than before

Considering each reading point the $R-S_1$ interval also increased after t_{AP} revealing a cyclic pattern during uterine contraction which was more pronounced after PCB (Table II) The increase did not correlate with AP Using the reading point 40 s before t_{AP} as a reference the increase was not statistically significant before PCB After PCB the increase was statistically significant at 10 and 40 s after t_{AP}

There was no statistically significant correlation between the $R-S_1$ and R−R intervals

In the fetus with PCB bradycardia the $R-S_1$ interval varied between 32 5 and 35 ms before PCB and between 35 and 37 5 ms afterwards In one case (Fig 2) variable decelerations (9) were registered during the second stage of labor and the $R-S_1$ interval increased from 30 ms between contractions to 37 5 ms during decelerations The umbilical cord of the newborn was tightly encircled around the neck One of the cases excluded due to FPCG noise before PCB had typical variable decelerations starting some 40 minutes after PCB the $R-S_1$ interval increased from 30 ms between contractions to 42 5 ms during decelerations

S_1 **amplitude** The S_1 amplitude was increased by a mean of 3 8 per cent after PCB A cyclic pattern was seen during contractions with the lower values after

Table III *Amplitude of the two parts of the first heart sound* S_{Ia} *and* S_{Ib} *at each reading point befor after PCB mm means and standard error of the means SE*

		Reading points (seconds)								
		−40	−30	−20	−10	t_{AP}	+10	+20	+30	+40
Before PCB										
S_{Ia}	mean	14 2	13 9	14 2	13 8	13 2	14 3	12 4	12 8	11 9
	SE	1 6	1 2	1 5	1 4	1 5	1 7	1 2	1 3	1 5
S_{Ib}	mean	12 9	12 5	12 1	11 4	11 6	10 2	10 4	10 6	10 9
	SE	1 0	0 9	0 9	0 8	0 7	0 7	0 7	0 7	0 8
After PCB										
S_{Ia}	mean	15 8[a]	15 8	16 1	15 4	13 7	13 4	13 8	12 2	13 2
	SE	1 3	1 5	1 6	1 8	1 4	1 5	1 4	1 2	1 2
S_{Ib}	mean	11 1	10 7	10 5	10 7	10 4	9 3	9 3	9 1	9 8
	SE	1 0	0 9	0 7	0 7	0 7	0 6	0 6	0 7	0 8

Statistical comparison see footnote to Table II

t_{AP} (Table III) The decrease after t_{AP} was not statistically significant before PCB After PCB the S_{Ia} amplitude was significantly lower 30 and 40 s after t_{AP} than 20 30 and 40 s before t_{AP}

In the fetus with PCB bradycardia the heart rate was constant for a short period during maximal bradycardia with R−R interval 692 5−700 ms (87−86 beats/minute) The S_{Ia} amplitude and the S_I-S_2 interval during this period showed a distinct variation Measuring 14 consecutive heart cycles the *correlation between these parameters was significant* statistically $r=0\,88$ $p<0\,001$ $y=0\,37x + 223$ ($S_{Ia}=x$)

S_{Ib} amplitude The mean values at each reading point were lower after PCB than before (Table III) Before PCB the means 10 20 and 30 s after t_{AP} were significantly lower than 40 s befor t_{AP} The same statistically significant changes were found after PCB

S_2 amplitude The amplitudes of A_2 and P_2 … analyzed separately After PCB the A_2 amp… showed a small statistically insignificant fall Th… amplitude did not change after *PCB* No cycl… tion of the A_2 or P_2 amplitudes took place

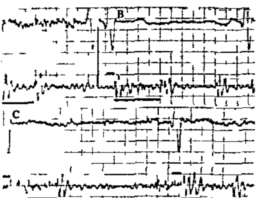
Uterine contractions Twenty patients received … ytocin infusion during the experiment to secure … uterine activity (Table I) Before PCB AP … from 27 to 99 mm Hg after PCB from 30 to … Hg AP did not change significantly after PCB (… IV) *but the frequency of contractions de…* ($p<0\,01$) The duration of the phases of the … pressure curve changed after PCB (Table I… found previously (12)

Forty s before t_{AP} the amniotic fluid press… not increased significantly in any patient The… at this reading point therefore represents the … culatory status in the fetus between contractio…

Table IV *Uterine contractions before and after PCB duration of phases seconds active pressure (AP) … Hg maximal rate of pressure increase (dP/dt max) mm Hg/s and frequency number of contractions p… minutes means and standard error of the means SE*

	A_a	A_r	A_d	D_a	D	$A+D_a+D_r$	AP	dP/dt max[d]	F
Before PCB									
mean	21 8	4 0	13 5	12 5	4 7	55 3	50 9	3 0	5 3
SE	1 7	0 8	1 2	1 0	1 1	2 0	4 0	0 2	0 2
After PCB									
mean	14 3	8 3[c]	11 2[b]	8 2	8 1	49 5[b]	54 3	2 6[b]	4 7[c]
SE	0 9	0 7	0 7	0 6	0 9	1 6	4 3	0 ?	0 2

A_a acceleration phase A_r rectilinear phase A_d deceleration phase of the ascending limb (A) of the amniotic pressure curve D_a acc… phase D_r rectilinear phase of the descending limb (D) of the amniotic pressure curve (12) Statistical comparison see footnote to Ta… [d]before statistical comparison two cases were excluded because the difference between AP before and after PCB was more than 5 … (dP/dt is proportional to AP (12))



Case 18 25 min after PCB fetal head on pelvic floor ...vy lines between the FECG and FPCG curves show the ...S_1 interval duration below FPCG curve heavy lines ...te the S_1-S_2 interval duration
... 20 s before t_{AP} $R-S_1$ interval 40 ms $R-R$ interval ...ms S_1-S_2 interval 195 ms
...0 s before t_{AP} $R-S_1$ 32 5 ms $R-R$ 625 ms S_1-S_2 210
...0 s after t_{AP} $R-S_1$ 35 ms in the first 40 ms in the se... cardiac cycle $R-R$ 800 ms S_1-S_2 232 5 ms Note ... $R-S_1$ interval increase in second heart cycle in C due ...eased amplitude of the first deflection of S_1 The ...ialy is disclosed by counting the number of deflections ...a and controlling the duration of S_1

DISCUSSION

... $R-R$ interval increased after PCB but ...ficantly so only after t_{AP} In patients where the ...dings were continued the $R-R$ interval had re...d the level before t_{AP} 10–20 s after the last ...ng point A corresponding fall of fetal heart rate ...ig uterine contraction after PCB was found in an ...r study (14) where the last reading was taken at ...nd of contraction to disclose late decelerations ...his time the fetal heart rate had almost reached ...alue it had before contraction Thus it seems that ... favors the development of early decelerations ...veral of the parameters measured showed an ob...s cyclic variation during uterine contraction The ...rn was not entirely regular but generally speak... he $R-R$ and $R-S_1$ intervals and to some extent ...S_1-S_2 interval increased after t_{AP} The S_{1a} S_{1b} ...A_2 amplitudes decreased after t_{AP} The cyclic ...ations were greater after PCB than before Organ ... (17) found that PEP increased during uterine ...raction in a similar manner to the $R-S_1$ interval ...he present study

The same cyclic variation of the S_{1a} amplitude and $R-S_1$ interval during uterine contraction was found in the ectopic beats of a fetus with supraventricular extrasystoles (13) A transfer of blood between the placenta and fetus and/or increased resistance of the fetal placental circulation was believed to cause the changes the ectopic beats being more sensitive to the hemodynamic changes than the sinus or postectopic beats which did not show cyclic variations

If PCB brings about a centralization of blood in the fetus the transfer of blood between the fetus and placenta would be enhanced explaining the increased cyclic variations observed during uterine contraction after PCB

Acidosis prolongs PEP (16) and reduces contractility (1) thus prolonging mechanical systole Acidosis after PCB could explain the prolonged $R-S_1$ and S_1-S intervals PCB with a small dose of local anesthetic (lidocaine 100 mg with or without adrenaline) injected *superficially* gave a fall of fetal scalp blood pH and increased pCO_2 (10) Signs of metabolic acidosis did not develop The fetal acidosis probably was secondary to a transitory acidosis in the mother It seems likely that maternal metabolic acidosis developed before PCB is masked by a respiratory alkalosis due to hyperventilation The pain relief of PCB suddenly removes hyperventilation revealing the metabolic acidosis

Teramo in 2 studies (21 22) injected larger doses of local anesthetic (mepivacaine 200–400 mg or bupivacaine 50–100 mg) *deeply* into the paracervical tissue and afterwards found increased base deficit together with pCO increase and pH fall This technique obviously may induce a fetal metabolic acidosis As several mothers in the present investigation had subjective symptoms and objective signs of a respiratory alkalosis before PCB acid base changes such as those reported by Jacobson and Gårdmark (10) most likely occurred in the fetuses Symonds (20) showed that fetal acidosis is correlated with a shift of the QRS axis to the left As the present series did not show any QRS axis change after PCB acidosis of the fetuses must have been slight

Many authors have reported a shortening of PEP during hypoxia in the fetus (17 18 23 26) The $R-S_1$ interval increased after PCB Even if the $R-S_1$ interval constitutes only a part of PEP it is unlikely that a shortening of PEP would have occurred simultaneously as those parameters largely describe the same physiological processes Murata *et al* (16) in their extensive in vivo studies of the fetal

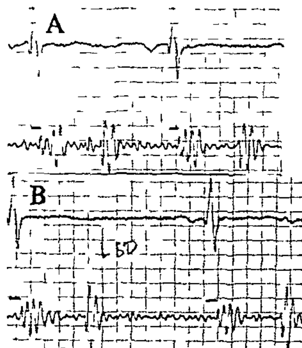


Fig 2 Case 20 The newborn infant had the umbilical cord tightly encircled around its neck The heavy lines between the FECG and FPCG curves denote the duration of the $R-S_1$ interval
A 50 s before t_{AP} $R-S_1$ 30 ms R−R 475 ms S_1-S 215 ms
B 10 s before t_{AP} $R-S_1$ 37 5 ms R−R 680 ms S_1-S 2‹7 5 ms

monkey found a small increase of PEP during nonacidemic hypoxia However in spite of a substantial pO_2 fall they found no direct correlation between PEP and pO_2

The prolonged $R-S_1$ and S_1-S intervals after PCB might be caused by a direct effect of the local anesthetic on the fetal heart Increased cardiac contractility as evidenced by the increased S_{1a} amplitude (19) and the unchanged relationship between the R−R and S_1-S intervals during early decelerations before and after PCB discount this possibility The variation of the S_{1a} amplitude and S_1-S_2 interval during PCB bradycardia with a constant R−R interval also speaks in favor of undisturbed myocardial contractility The ventricles are heterogenous with regard to muscle mass fibre orientation oxygen tension and catecholamine distribution (6) Variation of those factors might cause the beat to beat variability of fetal cardiac inotropism which was found A toxic effect of local anesthetic would probably have muted this variation

After late clamping of the umbilical cord a prolongation of PEP (25) and the S_1-S_2 in been found Accordingly a centralization of th blood volume would also prolong the S_1 bably the $R-S_1$ intervals A combined direct cardial influence of the local anesthetic tralization of the fetal circulation the best explanation of the changes found af

Yao *et al* (24) have shown ly transfered from the placenta to the inf though the circulatory dynamics before livery cannot be directly compared their resul that blood can most probably be transfered b the placenta and the fetus during uterine when the filling of the intervillous imum The periods of filling of the intervill (Fig 3) when the veins draining the are closed and the arteries filling it are open, cur during the periods of uterine PCB has lowered the rate of amniotic p change In this case the filling periods af would be prolonged increasing the impact tal circulation But the moments of arter venous closure or opening are unknown the duration nor the time of the filling periods determined

In vitro studies of arteries from the hu

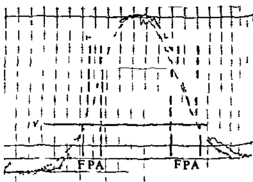


Fig 3 Case 8 Amniotic pressure curve of before PCB (dotted curve) superimposed on a curve of equal maximal amniotic pressure after PCB tinuous curve)
V arbitrary level of amniotic pressure at which the draining the intervillous space close on the and open on the descending limb of the amniotic pr curve A the corresponding pressure for the arteries the intervillous space FPB the filling periods of villous space before PCB FPA the filling periods PCB

Even if the pressure gradient between V and A temporal localization varies FPA will be longer than V or A do not change to any great extent after PCB

(5) and in vivo experiments in ewes at term
rterial injection of local anesthetic (7) have
that local anesthetics due to arteriospasm
ecrease both placental and nonplacental uterine
flow As the cyclic variations of the fetal sys
me intervals found is believed to be caused by
on of the intervillous space volume during uter
ntraction arteriospasm probably did not occur
present series Decreased arterial flow would
the intervillous space filling velocity and
se the cyclic variations after PCB

the whole the hemodynamic changes after
as judged by the method applied in the present
are small excluding any substantial depression
fetal cardiac function

ger doses of local anesthetic (21 22) are not
ary to achieve a sufficient analgesic effect and
be avoided With the technique and dosage of
anesthetic applied PCB is considered to be a
ethod of pain relief during the first stage of
in normal parturients

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A COMPARISON OF THE THREE METHODS FOR EXTERNAL FETAL CARDIOGRAPHY

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ract Phonocardiography abdominal electrocardio-
iy and ultrasound cardiography are the three methods
xternal fetal cardiography In the present study the
ods ha e been compared regarding the quality of the
s The patients (163) were between the 34th and the
week of gestation Graphs with less than 15 per cent
e or artifacts were found in 23 4 per cent for phono-
ography 55 2 per cent for abdominal electrocardio-
iy and 85 9 per cent for ultrasound cardiography It
l be shown that the number of successful abdominal
ocardiograms was higher with advancing gestational
The quality of the phonocardiograms was influen ed
sely by an anterior placenta No obvious influence of a
abdominal wall on external cardiography could be
nstrated

iotocography is one of the methods of surveil in the antenatal period Contrary to the situa during delivery one is entirely dependent on ex l methods for fetal heart rate monitoring i e ocardiography ultrasound cardiography and minal electrocardiography

ice the beginning of this century efforts have made to develop a phonocardiograph (21) The al use of phonocardiography became routine ig the 1960 s (7) Ultrasound cardiography was loped some years later (3 14) The first commer available equipment for abdominal electrocar raphy was introduced in 1974 (2 4 6 8 20) t cardiotocographs of today integrate all three iods for external cardiography in the same unit ie clinical use and practical application of each mal method have been investigated in many stud l 5 9 10 12 13 16 17 19) but only in a few has mparison of the three methods at the same occa and on the same patient been performed (1 10) he aim of this study was to compare the three dif nt external methods at the same time on the same l with special reference to the influence of the ental site and obesity

MATERIAL AND METHODS

During 18 months 163 antepartum recordings were obtained from 137 patients One hundred and fifteen patients were monitored once and 22 two or three times with at least one week s interval All patients were hospitalized and the re cordin s were obtained between 34 and 40 weeks of preg nancy The patients were monitored between 1 and 5 p m and the woman adopted a lateral tilt of some 15 with a pil low under the right side of her ba k Usually the bladder was emptied before the onset of registration

The length and weight of the patients were registered Obesity was d fined as more than normal mean weight + 20 per cent (15) The position of the fetus the maximal recor ding of the fetal heart sounds and the best pla e for the car diography transdu ers were marked on a chart In 143 cases the placental site was determined ultrasonically

A Hewlett Pa kard cardiotocograph model 8030 A was used equipped with heart sound transdu er 1513 B ultra sound transducer 15 7 A (broad beam transdu er) and an indifferent thigh electrode 15270 A For abdominal cardio tocography disposable ilver electrodes were used The caudal electrod was pla ed in the midline above the sym physis The cranial electrode was placed over the uterine fundus where the best fetal compl x was found The three methods of indirect cardiography were applied for 30 min ea h After the initial appli ation of the transducers (or electrodes) no further adjustment was made The paper speed was 1 cm min All records were obtained and examin ed by the author The percentage of artifa ts or failures were expressed as follows

$$\frac{\text{cm failure}}{\text{cm registration}} \times 100$$

The quality of the records was classified a cord ng to Ruttgers (17)

< 5 % failure = ery good quality
\> 5 < 15 % failure = good qual ty
\> 15 < 50 % failure = poor quality
\> 50 % failure = uninterpretable

RESULTS

An acceptable graph (very good or good quality) was obtained in 92 6 per cent of the 163 cases with either one or more of the methods In only 23 cases (14 per cent) however did all three methods succeed on the same occasion Phonocardiography gave very good

Table I *Quality of phonocardiograms from 163 cases between 34 and 40 weeks of pregnancy*

Quality	per cent	no
<5% failure	2 5	4
>5<15% failure	20 9	34
>15<50%	36 8	60
>50% failure	39 8	65

or good records in 23 4 per cent (Table I) The corresponding figures for abdominal electrocardiography and ultrasound cardiography was 55 2 and 85 9 per cent respectively (Table II and III) In only one case was phonocardiography the only working method, compared with 9 for abdominal electrocardiography and 52 for ultrasound

For phonocardiography the number of acceptable graphs never exceeded 32 per cent regardless of gestation From the 37th week abdominal cardiography succeeded in about 70 per cent Ultrasound gave good results regardless of the gestation (Fig 1)

The placenta was localized by ultrasound scanning in 143 cases Seventy seven cases had anterior and 66 posterior placenta The quality of the tracings obtained by phonocardiography was significant lower with anterior compared with posterior placentaes (Fig 2) No such difference was found for abdominal electro and ultrasound cardiograms (Fig 2) Among the studied patients 38 were defined as obese The quality of the records from phono and abdominal cardiography seemed to be low in these obese groups (Fig 3) but there is no statistical difference Obviously obesity has no influence on the ultrasound cardiography

In abdominal electracardiography the fundal electrode was placed on the same side as the fetal abdomen in 58 per cent of the cases in the middle in 24 per cent and on the side of the fetal black in 18 per cent of the cases

Table II *Quality of abdominal elctrocardiograms from 163 cases between 34 and 40 weeks of pregnancy*

Quality	per cent	no
<5% failure	24 5	40
>5<15% failure	30 7	50
>15<50%	6 8	11
>50% failure	38 0	62

Table III *Quality of ultrasound cardiograms 163 cases between 34 and 40 weeks of*

Quality	per cent	no
<5% failure	42 3	69
>5<15% failure	43 6	71
>15<50%	11 0	18
>50% failure	3 1	5

DISCUSSION

The study was restricted to pregnant the 34th and the 40th week of pregnancy T the investigation was to study all three ods for cardiography it has been shown prev that the abdominal electrocardiography will results during the 28th to 34th week (4 5 8 9 1

Under optimal conditions external me be compared on the same patient at the This can be done only for two methods simul ly (13) It is impossible to place all maximal point at the same time and consequen three methods have to be used after one was done in this study

The reported results of phonocardiography widely between 22 and 77 per cent tracings able quality (10 16 19) This may in part ed by different methods of evaluation same mode of interpretation as Rüttgers (17 per cent of the graphs in this study were fo

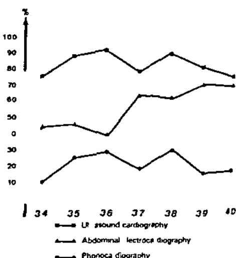
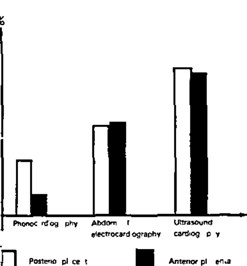


Fig 1 Comparison of the three methods of diography related to gestation The abscissa shows of pregnancy and the ordinate the percentage of gra less than 15 per cent failure



2 Comparison of cardiograms with <15 per cent re from 66 cases of posterior placenta and 77 cases of ior placenta

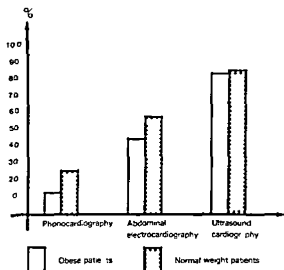


Fig 3 Comparison of cardiograms with <15 per cent failure from 38 patients with obesity and 125 patients with normal body weight

ery good or good quality Phonocardiography fore gives a higher number of poor or uninter able graphs than the other two methods

e difficulties with this method are also illustrated e fact that in only one case when ultrasound and minal electrocardiograph failed did phonocar raphy give an acceptable recording From these ts the need for phonocardiography as standard pment on cardiotocographs can be questioned

ith ultrasound cardiography very good or good rdings were obtained in 85 8 per cent The Dop signal however is rather undefined and of con able variation (1) The equipment used in this calculates the heart rate based on the mean fre cy of three beats consequently beat to beat ability is not calculated

bdominal electrocardiography will produce als defined enough to calculate beat to-beat vari ty (11) therefore in the interpretation of the ability this method gives a more reliable result ultrasound cardiography In the latter weeks of nancy especially the number of very good and d tracings is high and abdominal electrocardio- should be complementary to ultrasound

he placental site has some influence on the signals xternal cardiotocography (16 18) In agreement other reports (5 9) this study showed no obvious ence from the placental site on the quality of ab- inal electro- and ultrasound cardiography but e was a high number of poor and uninterpretable phonocardiograms when the placenta was situated anteriorally

The influence of a thick abdominal wall on exter nal cardiography is not quite clear (5 18) In this investigation no obvious influence could be demon strated

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ABRUPTIO PLACENTAE — TREATMENT WITH THE FIBRINOLYTIC INHIBITOR TRANEXAMIC ACID

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tract Abruptio placentae is known to have a bad prog s for the fetus Pathologic proteolysis e g a pathologic vation of the coagulation mechanism and/or the inolytic system is known to be a common complication ich cases Analysis of the coagulation factors and com ents of the fibrinolytic system in the acute stage of 14 s confirmed the earlier finding of mainly an activation ie fibrinolytic system which argues for the use of a spe fibrinolytic inhibitor 73 consecutive cases of abruptio ,entae were treated with tranexamic acid in the acute 67 of the patients were immediately delivered by ce in section The remaining six patients were in early ges nal age and were treated for a prolonged period The iatal mortality of the entire group was only 8 per cent the maternal mortality nil None of the cases were com ted by hemorrhagic diathesis or thromboses We be that routine immediate treatment with tranexamic acid educe the perinatal mortality in cases of abruptio pla ie

iptio placentae is known to have a bad prognosis he fetus Perinatal death rates of 33 to 37 per have been reported most of the fetuses being on admission (11 20) Also maternal deaths (2 I 21 22) have been reported Pathological pro 'sis i e a pathological activation of the coagula mechanism and/or the fibrinolytic system is vn to be a common complication (21) Recent es have produced evidence that activation of the nolytic system is often the predominant factor (6 This prompted us to try to reduce the complica s associated with abruptio placentae by treatment the fibrinolytic inhibitor tranexamic acid This r reports a consecutive series of 73 cases treated tranexamic acid in the acute stage before deliv or for a prolonged period in women in an early e of pregnancy

MATERIAL AND METHODS

39? deli eries 73 were complicated by abruptio placen These 73 women were given in the acute stage at admi 1 g of tranexamic ac d intra enou ly just before deli by cesarean sect on Six of the patients were in an early of pregnancy with less pronoun ed symptom In these oral treatment with tranexamic acid in a dose of 1 g × 4 a day was continued until delivery (Table III) which also was performed by cesarean section The diagnosis of abruptio placentae was confirmed at examination of the placenta after delivery Blood samples for determination of coagula tion factors and components of the fibrinolytic system were obtained from 14 of the patients

Laboratory methods Normal values refer to ·0 normal women in the 3rd trimester

Activated Partial Thromboplastin Time (APTT) Automated APTT (General Diagnostics) Normal value <40 sec

Platelet count according to Björkman (3) Normal value 130 000–362 000 mm³

Fibrinogen The blood was collected with epsilon aminocaproic acid (EACA) and the fibrinogen was measured with the method of Nilsson and Olow (18) Normal value 4 4±0 7 g/l

P&P complex (prothrombin + factor VII + factor X) was measured with the method of Owren and Aas (19) Normal range 124– >200 per cent

Factor V levels were measured with the method of Wolf (24) Normal value 104±12 per cent

Factor VIII activity (VIII C) was estimated according to Nilsson *et al* (16) Normal value 213 4±10 6 per cent Factor VIII antigen (VIII R Ag) was determined according to Holmberg and Nilsson (12) Normal value 269 6±20 2 per cent

Fibrinolytic activity of resuspended euglobulin precipitate on unheated fibrin plates (17) Normal value 0–65 mm²

Fibrin/fibrinogen degradation products (FDP) were measured with the immunochemical method of Nilehn (15) In the presence of EACA and thrombin this method will not show any FDP in serum from normal pregnant women who have a level of less than 5 g/l

Ethanol gelation test according to Godal *et al* (10)

Antithrombin III was determined immunochemically by the method of Fagerhol and Abildgaard (8) Normal value 98±7 per cent

Plasminogen was measured by an immunochemical method according to Ekelund *et al* (7) Normal value 121± 0 per cent

Alpha₂ macroglobulin was measured with the estrolytic method of Ganrot (9) Normal value 134± 4 per cent

RESULTS

Of the 73 consecutive cases of abruptio placentae the fetus in four was dead on admission All the patients were delivered by cesarean section 67 in the acute

Table I *Coagulation factors and components of the fibrinolytic system*

Patient no	Thromb	Fib g/l	F VII C/ F VIIIR Ag (%)	FV (%)	P&P (%)	APTT sec	Ethanol gelation	Plasm rogen
1 MS	230 000	5 4	213/209	100	>200	36	negative	100
2 KBD	170 000	3 2	100/164	98	108	36	negative	95
3 MH	165 000	3 6	290/400	105	124	32	negative	120
4 IF		4 4	153/240	109	192	38	negative	130
5 IG	260 000	5 1	311/	107	117	30	negative	100
6 IN		5 1	130/236	131	160	40	negative	170
7 DSC			/					140
8 SK		3 0	195/180	103	97	36	negative	176
9 KP	230 000	2 8	220/137	85	89	40	negative	130
10 EL		4 4	203/248	93	172	32	negative	135
11 LJ		2 7	142/160	125	136	42	negative	80
12 BS	250 000	3 9	213/260	147	101	37	negative	90
13 MF		4 5	370/336	105	184	35	negative	150
14 AS		1 7	140/400	61	128	36	negative	60

Table I *Continuation*

AT III (%)	α_2 macro (%)	Euglobulin precipitate (lysed area mm^2)	FDP g/l
100	116	25	10
88	124	69	12
78	107	10	9
100	128	90	0
120	133	10	11
90	147		16
	113		39
70	106	36	76
112	134	130	11
80	122	46	0
60	137	38	0
90	149	49	0
135	175	10	13
55	75	31	60

stage and six after treatment with tranexamic acid for 3–32 weeks Two neonates in the acute group were in a bad condition when delivered and did not survive i e a total perinatal mortality of 8 per cent The maternal mortality was nil The clinical data on the six patients treated for a prolonged period with tranexamic acid are given in Table III The neonates had an Apgar score of 8–9 at 60 sec after birth No case of hemorrhagic diathesis thrombotic complications or perinatal death occurred in this subgroup

The values of coagulation factors and components of the fibrinolytic system examined in the acute stage in 14 of the patients are given in Table I The concentration of fibrinogen was low in six cases FDPs were found in blood in ten of the patients and low plasminogen levels were found in six Four patients had somewhat low P&P levels and factor VIII activity and antigen were slightly depressed in some cases

The ethanol gelation test was negative in all. count factor V and AT III were within the range with the exception of case 14 The fin follow up of two of the cases (9 and 12 in during the treatment with tranexamic acid in Table II During treatment FDP disappea the fibrinogen levels increased as did the co tion of plasminogen No changes in the oth ulation factors occurred

DISCUSSION

Of the 73 cases of abruptio placentae trea tranexamic acid none were complicated by rhagic diathesis and the perinatal mortality w per cent Of the 14 patients in whom coagula tors and fibrinolytic components were meas admission the concentration of fibrinogen P&P complex were low in some but the gelaton test was negative and the platelet co normal The plasminogen levels were somew and FDP occurred in most cases These find not compatible with a marked intravascular tion or consumption coagulopathy but above all activation of the fibrinolytic sys em also emphasized by the findings given in Tab which cases the concentrations of fibrinog plasminogen rose during treatment with tra acid while FDPs disappeared The results are trast to the conclusion of Sher *et al* (22) that rhagic diathesis was due to consumption co pathy in 10 per cent of his cases of abrupt centae However he also reported in reased

e II *Coagulation factors and fibrinolytic components during therapy with tranexamic acid*

no	Throm	Fib	F VIII C/ F VIIIR Ag	FV	P&P	APTT	Ethanol gelation
before treatment	230 000	2 8	220/137	85	89	40	negative
during	410 000	3 6	175/155	92	196	38	negative
treatment		4 5	240/138	60	90	39	negative
before treatment	250 000	3 9	213/260	147	101	37	negative
during	225 000	4 7	130/212	170	92	38	negative
treatment	245 000	5 0	400/292	174	136	35	negative

e II *Continuation*

m n	AT III	α_2 macro	Euglobulin precipitate	FDP
	112	134	130	11
	80	125	51	17
	82	91	10	0
	90	149	49	0
	80	141	29	0
	110	154	10	0

ons of FDPs in his cases Edgington (6) used the age associated neo antigen of fibrinogen for dif tiation between FDP derived from respectively nogen and fibrin In all his cases of abruptio ntae the FDPs were derived from fibrinogen on hus indicating above all activation of the nolytic system

ring pregnancy fibrinolytic activity sucessively ases and rapidly returns to its original level after ation of the placenta We have shown the sig nce of the placenta in depression of the fibrino activity (25) The activation of the fibrinolytic n in these cases can be explained by release of inogen activators from the uterus which is n to be rich in such enzymes (1) together with ased inhibition by placenta when partly sepa

Sher (22) used the protease inhibitor Trasylol[R] and reported a good effect of such treatment Astedt and Nilsson (26) have reported a case of recurrent abruptio placenta successfully treated with tranexamic acid

Some authors feel that depression of fibrinolytic activity by administration of inhibitors during preg nancy might be hazardous (4 23) For the apparently paradoxical non thrombogenic effect of tranexamic acid there are probably several explanations In a series of patients receiving AMCA (tranexamic acid) for 2 weeks in a dose of 4 g a day we examined the fi brinolytic activity in vein biopsy specimens histo chemically before and on the last day of treatment Tranexamic acid did not suppress the content of fi brinolytic activators in the vessel wall (unpublished data) Neither did any thrombotic complications oc cur in Klimek and Stanek (13) series of 92 patients with threatening abortion and treated for a long duration with epsilon aminocaproic acid

The finding in the present investigaiton of an ac tivation of mainly the fibrinolytic system speaks in favor of the use of a specific fibrinolytic inhibitor Tranexamic acid given immediately might have prevented further activation of the fibrinolytic system since none of the patients developed hemorrhagic di athesis We therefore believe that routine immediate treatment with tranexamic acid can reduce the perina tal mortality in cases of abruptio placentae

e III *Clinical data on the patients treated with tranexamic acid*

no	Acute symptom of abruptio placentae (week of pregnancy)	Therapy with tran examic acid (weeks)	Cesarean section (week of pregnancy)	Apgar score (1 min te)
	35	3	38	8
	26	12	38	9
	32	1	33	9
	32	4	36	9
	27	10	37	8
	29	5	34	9
Mean	30 2	Mean 5 8	Mean 36	Mean 8 7

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RISK OF SPONTANEOUS ABORTION FOLLOWING LEGALLY INDUCED ABORTION

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act Using the registration of all pregnant women liv ithin a particular geographical district of Copenhagen isk of spontaneous abortion has been calculated by s of a decremental method A total of 3 042 pregnan vere registered and the total risk of spontaneous abor was calculated at 10 per cent In 431 women the previ pregnancy had been terminated by a legally induced ion Increased risk of spontaneous abortion could not monstrated in this group where the cumulative risk of taneous abortion was 12 per cent In particular the risk e abortion was not seen to increase

risk of spontaneous abortion was found to be lated with the woman s age by Shapiro & mowicz (9) and Petterson (6) Petterson (6) d the risk of spontaneous abortion minimal at 26 s and increased before and after this age In ad n the outcome of previous pregnancies were d to correlate with the risk of spontaneous abor Thus Petterson (6) as well as Warburton & r (11) found the risk of spontaneous abortion r in women with previous spontaneous abor than in others

e reasons for spontaneous abortions are often abnormalities Lauritsen (5) found chromosome mities in 61 per cent in the first trimester In cases the reason must be sought in uterine mal ations or in so-called cervical insufficiency

ice the mid sixties legal abortion is being asingly used in a number of Western countries as Denmark Great Britain Sweden and the A and so it is of even greater interest to study her a legally induced abortion increases the risk mplications including the risk of spontaneous tion in the next pregnancy

the basis of a register of all pregnant women n one geographical district the present study to evaluate if there is an increased risk of spon ous abortion in women whose previous pregnan as terminated by legal abortion

MATERIAL AND METHODS

The study included all women who delivered or aborted within the period 1st February 1975 to 31st January 1977 with a permanent address at Frederiksberg an independent administrative unit in the center of Copenhagen On 1st January 1976 there were 93 692 inhabitants including 16 857 women 15-45 years This municipality was consider ed suitable for the study as the population figure was stable and the population was mainly referred to only one hospital

The study is prospective and based upon data recorded in connection with abortion or delivery In order to secure a complete record of all pregnancies data were collected in four different ways

1 All women admitted to the local hospital for delivery or abortion were registered

2 All deliveries in maternity homes were registered as it was possible to trace these women via the municipal ac counts department

3 All practioners of this district reported on all pregnancies which did not lead to admission to the local hospital

4 At the pharmacies in the district all women who had a positive pregnancy test received a letter asking them to co-operate in the study and to return a post-card enclosed stating name address and telephone number Eight women registered by the practioners and 352 women registered by *the pharmacies were then contacted on telephone or at their* address if they were not registered by the local hospital Through these two channels 11 women were registered who were not registered by the hospital at the same time

In this study period 3 042 pregnancies were registered 1 667 deliveries 210 spontaneous abortions 17 extrauterine pregnancies and 1 148 legal abortions

On the basis of patient records and interviews the follow ing data were recorded

Date of deli ery previous pregnancies and their outcome date of last menstrual period date of the termination of the pregnancy gestational age estimated by the size of uterus at the first gynecological examination of the current pregnan-cy and the outcome of the pregnancy whether delivery spontanoues abortion extrauterine pregnancy or legal abor tion

Spontaneous abortions were defined as registered preg nancies confirmed either by means of the presence of chorionic gonadotrophin or by histological examination which ended spontaneously before the end of 27th week of gestation with no signs of fetal movements

Table I *Number of registered pregnancies classified in age groups and pregnancy outcome ⸼ tion extrauterine pregnancy legal abortion or live birth The table also shows the cumulative risk of ous abortion calculated by means of the decremental method*

Age group	No of pregnancies		No of spontaneous abortions		No of extrauterine pregnancies		No of legal abortions		No of deliveries		Cumulative of abortion
< 21 years	349	100%	22	6 3%	1	0 3%	167	47 9%	159	45 5%	9 8%
21 30 years	1 938	100%	116	6 0%	11	0 6%	602	31 1%	1 209	62 3%	8 2%
> 30 years	755	100%	72	9 5%	5	0 7%	379	50 2%	299	39 6%	15 9%
Total	3 042	100%	210	6 9%	17	0 6%	1 148	37 7%	1 667	54 8%	10 0%

Cumulati e risk significantly greater than among women in age group 21 30 years $p<0\ 05$

The gestational age at the termination of the pregnancy was calculated from the last menstrual period In order to reduce the influence of an irregular menstrual pattern on the calculated gestational age the gestational age was also estimated by the size of the uterus at the first gynecological examination in the current pregnancy In those cases where there was a difference of more than 8 weeks between the two methods calculations of gestational age were bases on the size of the uterus

The woman s age was recorded as her age at the time of conceiving

The total patient data were classified according to the termination of the previous pregnancy and the following four categories were described

Group 1 Women whose previous pregnancy was terminated by a legal abortion 431 women

Goup 2 Women whose previous pregnancy had ended in spontaneous abortion or extrauterine pregnancy 254 women

Goup 3 Women whose previous pregnancy had ended in a delivery 1 171 women

Group 4 Women with no previous pregnancies 1 186 women

The sum of spontaneous abortions and extrauterine pregnancies was taken as the calculated risk of spontaneous abortion This risk was calculated by means of a decremental method All pregnancies within the study were considered as being under observation from the date of conception

The risk of spontaneous abortion in each group was compared by means of a generalized edition of Wilcoxon s test the so-called Gehan s test described by Gehan (3) 0 05 was regarded as the significance level

RESULTS

Table I shows the results classified according to age groups below 21 years 21 30 years and over 30 years The table indicates the distribution of pregnancy outcome as well as the cumulative risk of spontaneous abortion in the three age groups calculated by means of the decremental method There was no difference in abortion risk between the two younger age groups (9 8 and 8 2 per cent) whereas the *spontaneous abortion was greater* over 30 years per cent

Table II shows the risk of spontaneous the total number of patients calculated by the decremental method The cumulative r 10 0 per cent Table III has the equivalent group I The cumulative risk of spontaneous a was 12 0 per cent In addition table III shows 431 pregnant women of this group no abortions were registered after 18 weeks of

Table IV shows the cumulative risk abortion in groups 1 to 4 in the age years and over 30 years as the number of in the group under 21 years was too small the risk of spontaneous abortion in each of groups separately

In the age groups 21 30 years and over 3 there was no difference in the risk of abortion between group 1 and groups 2 3 Correspondingly no difference in risk of taneous abortion could be demonstrated groups 1 2 and 3 in women with only one pregnancy and neither when women in group only one previous pregnancy were women in group 4

DISCUSSION

This study demonstrated a cumulative risk of taneous abortion of 10 0 per cent The ri greatest in women over 30 years of age 15 The risk of spontaneous abortion was ca means of the decremental method have previously adopted this method to calcul risk of a pregnancy not ending in a live birth York 1958 1960 Shapiro and Abramowicz

II *Risk of spontaneous abortion in women living within the district of Frederiksberg pregnant in the pe*
st February 1975 to 31st January 1977

No of spontaneous abortions	No of induced abortions	Pregnant at beginning of the week	Exposed to risk of spontaneous abortion	Risk of spontaneous abortion	Cumulative risk of spontaneous abortion	Standard deviation
3	1	3 042	3 041 5	0 10	10 0	0 6
11	10	3 038	3 033 0	0 36	9 9	0 6
21	22	3 017	3 006 0	0 70	9 6	0 6
22	90	2 974	2 929 0	0 75	8 9	0 6
14	252	2 862	2 736 0	0 51	8 2	0 6
25	265	2 596	2 463 5	1 01	7 8	0 6
23	225	2 306	2 193 5	1 05	6 8	0 6
23	131	2 058	1 992 5	1 15	5 8	0 5
23	74	1 904	1 867 0	1 23	4 7	0 5
15	25	1 807	1 794 5	0 84	3 5	0 4
12	24	1 767	1 755 0	0 68	2 7	0 4
5	8	1 731	1 727 0	0 29	2 1	0 3
5	7	1 718	1 714 5	0 29	1 8	0 3
10	6	1 706	1 703 0	0 59	1 5	0 3
1	3	1 690	1 688 5	0 06	0 9	0 2
1	4	1 686	1 684 0	0 06	0 8	0 2
1		1 681	1 681 0	0 06	0 8	0 2
3	1	1 680	1 679 5	0 18	0 7	0 2
1		1 676	1 676 0	0 06	0 5	0 2
1		1 675	1 675 0	0 06	0 5	0 2
2		1 674	1 674 0	0 12	0 4	0 2
3		1 672	1 672 0	0 18	0 3	0 1
2		1 669	1 669 0	0 12	0 1	0 1

of 15 per cent of a pregnancy not ending in a irth and Taylor (10) fond in 1959 1960 in a pregnancy loss of 16 per cent In 1960 in a from New York in which the risk of spontane portion within the first weeks of gestation was ated by extrapolation Erhardt (2) found a ancy loss of 29 5 per cent In Sweden Petterson and a risk of spontaneous abortion of 14 per p to 27 weeks gestation

s study included all pregnant women living a certain district of Copenhagen All women egistered at the termination of their pregnancy isk of spontaneous abortion was calculated in a way that all women entered into the analyses the date of conceiving So the present results t be compared directly with the above mention dies in which a woman was admitted into the ses only from the moment the pregnancy was osed This particularly leads to a difference in alculated risk of spontaneous abortion during rst weeks of pregnancy when the deficit be- the number of lost pregnancies and the number stered spontaneous abortions must be expected greatest The reason is that abortions at such an date do not always make the women consult her r who would be able to make the diagnosis and also that such early spontaneous abortions will often not be recognized as an abortion by the woman her self The calculated risk of spontaneous abortion dur ing the first weeks must therefore be considered with reservations and taken as the minimum rate Only Erhardt s study (2) using extrapolation tried to estimate the pregnancy loss during the first weeks of pregnancy and his study reported a high estimate of pregnancy loss

Another factor which makes the calculation of risk of spontaneous abortion inaccurate is that some preg nancies are terminated by illegal abortion All the above studies were made in countries where abortion was not legalized therefore an unknown number of pregnancies would probably have been terminated by illegal abortion In all probability some illegal abor tions would be registered as spontaneous abortion making the calculated spontaneous abortion risk too high In Denmark all women have the right to have an unwanted pregnancy terminated before 12 weeks gestation so the number of illegal abortion will presumably be small However a situation of this kind may lead to another source of error A calcula tion of the risk of spontaneous abortion is based upon an indirect presumption that the pregnant women entering into the analyses at any time are a

Table III *Risk of spontaneous abortion in 431 women whose previous pregnancy had been gal abortion*

Week	No of spontaneous abortions	No of induced abortions	Pregnant at beginning of the week	Exposed to risk of spontaneous abortion	Risk of spontaneous abortion	Cumulative risk of spontaneous abortion	devi
5			431	431 0		12 0	2 0
6		2	431	430 0		12 0	2 0
7	6	7	429	425 5	1 41	12 0	2.0
8	4	11	416	410 5	0 97	10 7	2 0
9	2	51	401	375 5	0 53	9 8	2.0
10	3	48	348	324 0	0 93	9 3	2 0
11	4	36	297	279 0	1 43	8 5	1 9
12	2	30	257	242 0	0 83	7 2	1 8
13	3	15	225	217 5	1 38	6 4	1 7
14	3	5	207	204 5	1 47	5 1	1 6
15	4	7	199	195 5	2 05	3 7	1 4
16		3	188	186 5		1 6	0 9
17		2	185	184 0		1 6	0 9
18	3		183	183 0	1 64	1 6	0 9
19							
20							
21							
22							
23			180	180 0			
24							
25							
26							
27							

representative group This presumption will be correct only if the women with legal abortions have the same risk of spontaneous abortion as those whose pregnancy is continuing It is difficult to say to what extent this presumption is correct Women admitted to hospital with a threatened abortion and thus a high risk of spontaneous abortion may for instance choose to have an unplanned pregnancy terminated as a legal abortion rather than submit to prolonged confinement to bed Such a situation would result in an underestimate of the risk of spontaneous abortion

This study particularly tried to evaluate whether there was an increased risk of spontaneous abotion in women whose previous pregnancy had been terminated by a legal abortion The background of this theory was based upon two factors Firstly a presumption that dilatation of the cervical canal would result in lesions causing an increased risk of cervical insufficiency Wright *et al* (12) demonstrated an increased risk of cervical insufficiency in women with a previous legally induced abortion The second factor was that intrauterine changes such as a defective uterine cavity and synechia as may be seen after a legal abortion Krajl & Lavric (4) and von Seewald (8) might impede nidation and placental function with an ensuing risk of spontaneous abortion

The present study could not demonstra creased risk of spontaneous abortion in whose previous pregnancy had been term legal abortion The cumulative risk of abortion in this group was 12 0 per cent N the age group 21 30 years nor in women over was the risk of spontaneous abortion signi creased in women whose previous been terminated by a legal abortion when cor with women whose previous pregnancy had en a delivery or who had not been pregnant table IV It is of particular interest that afte abortion there were no spontaneous abortic than 18 weeks of gestation in the cy table III This finding does not support that legal abortion causes an increased risk of c insufficiency therefore we are not able to c the findings of Wright *et al* (12) Our results ar sistent with the findings of Daling & Eman who did not demonstrate an increased risk of s neous abortion in women with a previous in abortion In a retrospective study from Japan & Aoyama (7) demonstrated an increased freq of spontaneous abortions in pregnancies follow induced abortion as did Petterson (6) Most

ɔle IV *Cumulative risk of spontaneous abortion among women whose previous pregnancy ended in legally uceed abortion group 1 spontaneous abortion group 2 delivery group 3 and women without previous gnancies group 4*

	All pregnancies				Women with only one previous pregnancy		
	Group1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3
at conception 21 – 30 years							
o of previous pregnancies	n	n	n	0	1	1	1
o of pregnancies registered	245	153	738	802	110	71	458
o of spontaneous abortions	17	19	46	45	6	7	30
umulative risk of spontaneous ›ortion	9 6%	13 3%	7 8%	7 1%	6 9%	10 1%	7 9%
at conception > 30 years							
ɔ of previous pregnancies	n	n	n	0	1	1	1
ɔ of pregnancies registered	152	90	391	122	24	24	108
ɔ of spontaneous abortions	16	15	33	13	3	3	10
ımulative risk of spontaneous ortion	21 4%	21 6%	14 3%	12 8%	15 7%	15 0%	12 6%

> 0

tions in Petterson s study were however per ied by vaginal hysterotomy so his results do not pare directly with the results of this study made in mark where 9 per cent of all induced abortions performed by dilatation and curettage 82 per by the suction method and vaginal hysterotomy rdly used

CONCLUSIONS

population living within a well defined district of nhagen we found a cumulative risk of spontane abortion of 10 per cent by means of the mental method Related to age the risk was sig ntly greater in women over 30 years of age 15 9 ent than in women of the age group 21 30 years e the risk was 8 2 per cent The risk of spontane ibortion was not increased in 431 women whose ious pregnancy was terminated by a legal abor the cumulative risk of spontaneous abortion 12 0 per cent It is particularly interesting that in group there were no spontaneous abortions after eeks gestation

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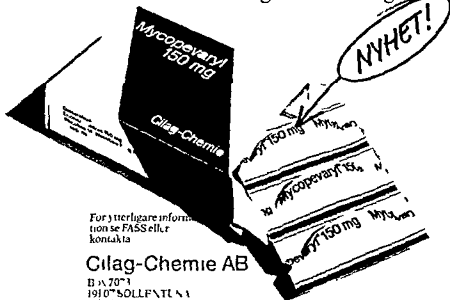


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HYPERPROLACTINEMIA IN CASES OF INFERTILITY AND AMENORRHEA

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tract Of 17 patients with longstanding (3 – 15 years n 7 7 years) amenorrhea and hyperprolactinemia 8 de ped their amenorrhea after the use of oral contracep (Group I) and 9 became amenorrhoic spontaneously oup II) There were no differences between the groups respect of the basal serum levels of FSH LH low polar ogens (estradiol 17β + estrone) and prolactin Tomogra revealed pituitary adenoma in four patients One of developed symptoms of her tumor during pregnancy ymptoms disappeared after delivery The other patients tumors are checked twice a year and have not yet re d any treatment The patients with no detectable tu s were treated with bromocriptine starting with 1 25 × ly The peripheral serum levels of prolactin FSH LH olar estrogens and progesterone were determined once k and if the prolactin levels remained high the bromo ne dose was increased All these patients started to truate as soon as prolactin returned to normal levels w 25 μg/l) All patients who wished to became preg i e 6 patients Three were delivered by cesarean sec one had a normal delivery and two are still pregnant ere was no difference between Group I and Group II in ose required or in the duration of treatment before truation started Three cases of galactorrhea were 1

71 Hwang and co-workers (7) described the first od for radioimmunological determination of ctin in peripheral human circulation Since then knowledge on the physiology of prolactin has in ed immensely The frequency of hyperprolactin is high among women suffering from amenor and anovulation Galactorrhea is not always pre in these cases It is supposed that hyperprolactin disturbs the normal menstrual cycle by interfer n the hypothalamic level with the positive feed of estrogens upon the release of gonadotrophins Women with amenorrhea due to hyperprolactin have no episodic LH secretion and do not res l to clomiphene treatment

has been found that about 30 per cent of the mophobic adenomas earlier considered to have unction are associated with a hypersecretion of ctin (4) These tumors are often difficult to diag l the visual fields are normal and so is the X ray re of the skull and sella turcica It is necessary to complete the examination with tomography The frequency of such tumors in cases of hyperprolactinemia has been discussed extensively but at least 30 per cent of the women with high prolactin levels have a pituitary adenoma (10) Bromocriptine (2 bromo-α ergo criptine) a longacting dopamine receptor agonist decreases prolactin levels Thus it is possible to restore the function of the ovaries and normal menstruations occur as long as the treatment continues Since the first report by Besser and co workers in 1972 (2) concerning treatment of amenorrhea and infertility with bromocriptine more than 100 reports have been published on this subject In Sweden Bergh and co workers (1) recently published a material of 42 women with longstanding amenorrhea who had been treated with bromocriptine Among them 24 had radiological signs of a pituitary tumor Twenty one out of 22 women who wanted to become pregnant conceived The present communication describes the results of treatment with bromocriptine in patients with spontaneous and post pill longstanding amenorrhea respectively

MATERIAL AND METHODS

Clinical Material For a long time now the routine investigation of patients with longstanding amenorrhea has included determination of peripheral serum levels or urinary excretion of gonadotrophins and estradiol 17β + estrone (LPE low polar estrogens) The patients had been examined once a year with hormone determinations and with respect to visual fields After the introduction of prolactin determinations in 1976 17 patients with amenorrhea lasting for more than 3 years were found to have high serum levels of prolactin (< 25 μg/litre) Eight patients (Group I Table I) developed their amenorrhea when they stopped taking combined oral contraceptives Nine patients (Group II Table III) had no demonstrable reason for their amenorrhea All patients were euthyroid

The patients were treated with bromocriptine (Pravidel(R) Sandoz A G) starting with 1 25 mg × 3 daily The serum levels of prolactin FSH LH LPE and progesterone were determined once a week and in cases were prolactine levels remained high the dose of bromocriptine was increased

Table I *Post pill amenorrhea (Group I)*

Case	Age	Duration of amenorrhea Years	X ray sella	Tomo graphy	Visual fields	FSH U/l	LH U/l	LPE pM	Prola [illegible]
1	45	7[a]	normal	normal	normal	4 2	7 8	172	45
2	42	12	normal	normal	normal	7 6	4 0		[illegible]
3	40	3[b]	normal	tumor	normal	4 1	15 5	108	>200
4	37	8	normal	normal	normal	4 2	7 9	130	>200
5	33	11	normal	normal	normal	18 5			[illegible]
6	30	6	normal	normal	normal	8 1	8 5	134	>200
7	28	5	normal	normal	normal	2 5	5 1	85	>200
8	28	11	normal	normal	normal	3 9		78	[illegible]
Mean±S D	35 4±6 6	7 9±3 2				6 6±5 1	8 1±4 0	117 8±34 9	

a) Galactorrhea b) Galactorrhea Poor response upon LH RH stimulation

Hormone analyses

Serum prolactin was determined by using a radioimmunoassay kit from CEA IRESORIN (Fleurus Belgium) The values are expressed as μg NIH (1) prolactin per litre

Serum levels of FSH and LH were determined by radioimmunoassay using the Double Antibody Solid Phase (DASP[(R)] Organon OSS Holland) separation technique Antibodies against FSH and LH as well as highly purified FSH and LH for iodination were obtained from KABI AB Stockholm Sweden The ^{125}I labelling was performed by the chloramine T technique described by Hunter & Greenwood (6) The values are expressed as units per litre of Human Pituitary FSH 68/39 and Human Pituitary LH or ICSH 68/40 respectively

Serum progesterone was determined radioimmunologically after extraction with n hexane (11) Anti progesterone 11α hemisuccinate bovine serum albumin (sheep) was obtained from The Royal Veterinary College Uppsala Sweden

Serum levels of low polar estrogens (LPE) were determined by the radioimmunoassay technique of Edqvist & Johansson (3) using an antiserum against estradiol 17β hemisuccinate bovine serum albumin (8) This antibody reacts to 100 per cent with estradiol 17β and to 50 per cent with estrone The values are expressed as pmol immunoreactive estradiol equivalents per litre

The intra and inter assay variations of the metho for prolactin 5 0 and 7 2 per cent for FSH 8 0 and 10 cent for LH 8 7 and 9 4 per cent for progesterone 11 11 5 per cent and for low polar estrogens 13 1 and 1 cent

RESULTS

The basal hormone values for Groups I and II en in Tables I and III There were no significa ferences between the mean hormone values two groups The values for FSH and LH co to those found during the follicular phase in menstrual cycle while the values for LPE ar same range as for postmenopausal women prolactin was elevated (>25 μg/l) in all cases In *Group I* (Table I) two women 45 and 4 age (patients 1 and 2) refused treatment with criptine They are being treated cyclically with gens and gestagens and checked twice a yea terminations of the visual fields and once a yea tomography of the sella One patient (No 3) ha tuitary tumor and also responded poorly to L

Table II *Results of treatment with bromocriptine (Group I)*

Case	Age	Dose	Duration†	Comments
1	45			Cyclic treatment with estrogens + progesterone
2	42			Cyclic treatment with estrogens + progesterone
3	40			Tumor not yeat treated
4	37	1 25×3×3 mo 2 5 ×4×2 mo	5 mo	
5	33	1 25×3	1 mo	
6	30	1 25×3×2 mo 2 5 ×3×3 mo 2 5 ×4×2 mo	7 mo	
7	28	1 25×3	1 mo	Stopped medication Menses disappeared Started agai Mens- returned Pregnant delivered in the 40th week
8	28	1 25×3	1 mo	Pregnant after 2 months of treatment Delivered in the 40th w

) Dose of bromocriptine in mg †) Duration in months before the first menses

[Tab]le III *Spontaneous amenorrhea (Group II)*

Age	Duration of amenorrhea Years	X ray sella	Tomography	Visual fields	FSH U/l	LH U/l	LPE pM	Prolactin µg/l
46	3	normal	normal	normal	13 7	11 0	179	>200
39	3 5	suspect	tumor	normal	5 2	9 6	81	50
33	12	normal	normal	normal	1 3	9 9	78	>200
33	8[b]	empty	tumor	normal	0 8	6 0	32	106
9	8	normal	normal	normal	6 7	10 0	39	98
29	14	normal	tumor[†]	normal	2 9	11 3	52	>200
25	7[d]	normal	normal	normal	9 7	14 5	110	>200
22	5	normal	normal	normal	4 7	9 4	55	107
21	5	normal	normal	normal	7 2	8 3		>200
±S D 30 8±8 1	7.3±3 7				5 8±4 1	10 0±2 3	78 4±48 0	

[Po]or response on LH RH stimulat on b) No response on LH RH stimulation c) Poor respo se on LH RH stimulation Galactorrhea [Re]fused treatment †) Detected during preg ancy

[stim]ulation The X ray of the sella was negative but [tom]ography revealed an enlarged sella turcica No [treat]ment has yet been given The other patients [(Tab]le II) responded to the treatment with normal [men]strual cycles Two of them (No 7 and 8) wanted [...] they conceived after 2 and 3 mon[ths] of treatment respectively They were delivered in [the 3]0th week of pregnancy patient 7 with cesarean [secti]on

[Grou]p II In patient 10 (Table III) tomography re[veale]d an asymetrically enlarged sella which had [sligh]tly increased at re-examination three months [later]. She is being treated with bromocriptine check[ed re]gularly and the visual fields are normal Patient [... w]as examined in 1975 and then did not respond to [LH] RH stimulation She was therefore examined at [the N]eurological Department of Karolinska sjukhus [in S]tockholm No changes in the sella were then de[tecte]d Upon re-examination two years later the se[rum] prolactin levels were determined and found to be elevated The sella was now examined with tomography and cisternography which gave evidence of a tumor without any supra-cellular spread The patient feels well and is not being treated She is examined every third month Patient 15 refused treatment because she did not believe in new drugs and did not want to be an experimental animal She is checked twice a year

All patients in this group who wanted to be pregnant conceived (No 13 14 16 17) Patient 13 aborted in her 12th week of pregnancy but got pregnant again one month later She is now in her sixth month of pregnancy Patient 16 is pregnant in the 20th week Patient 14 had galactorrhea now and had previously been treated 5 times with hCG and hMG She responded to that treatment with ovulation but did not get pregnant Prior to treatment with bromocriptine the visual field and sella X ray examination yielded normal results She started to menstruate after one month of treatment and conceived after two months

[Tabl]e IV *Results of treatment with bromocriptine (Group II)*

	Age	Dose	Duration†	Comments
	46	1 25×3	3 we	
	39	1 25×3	1 mo	Tumor
	33	1 25×3×6 we 2 5 ×3×3 mo	4 5 mo	
	33	–	–	Tumor No treatment
	29	1.25×3	1 mo	Pregnant Aborted in 12th week Pregnant again
	29	1 25×3	1 mo	Pregnant Delivered in the 36th week Tumor was found
	25	–	–	Refused treatment
	29	1 25×3	9 we	Pregnant
	21	1 25×3	2 mo	Pregnant Delivered in the 36th week Placenta previa

[Do]se of bromocriptine in mg †) Duration in week or months before the first menses

Her visual fields were examined once a month She complained of headache from the third month of pregnancy and in the sixth month defects in the visual fields appeared Bromocriptine treatment (10 mg daily) was then started A tomography in the 34th week showed that dorsum sella was very thin which could be explained by an intracellular expansive process In spite of the bromocriptine treatment the defects in the visual fields became enlarged the headache became worse and the sight of the left eye diminished considerably She was therefore delivered in the 36th week of pregnancy by cesarean section After the delivery the headache and the defects in the visual fields disappeared within 10 days and her sight became normal She stopped the bromocriptine treatment 1 month after delivery and started to breastfeed her baby Patient 17 had a placenta previa and was therefore delivered in the 36th week of pregnancy with cesarean section

DISCUSSION

The clinical material in this study included only patients who had been amenorrhoic for more than 3 years (mean 7 7 ±4 2 range 3–15) and who showed elevated prolactin but normal FSH levels In this small group we found 4 cases i e 23 5 per cent who had a pituitary tumor These patients should be carefully monitored during pregnancy and have their visual fields checked frequently because there is a risk that such tumors may grow rapidly during the last trimester inflicting damage to the optic nerve Such changes occurred in one of our patients but they disappeared almost immediately after delivery

The frequency of hyperprolactinemia among all our cases of amenorrhea is difficult to evaluate as we have determined the prolactin levels in all new patients but also among our cases with longstanding amenorrhea who are re examined once a year at our department Longstanding post pill amenorrhea has been attributed earlier to a persistent disturbance in the hypothalamus as a result of the pill intake One hundred and seventy seven patients with post pill amenorrhea have previously been examined endocrinologically and followed up by us (5) Spontaneous cure followed in almost 90 per cent of the cases within 5 years Among the patients who still were amenorrhoic 8 patients lived in Stockholm and could be re examined All of them had hyperprolactinemia and one of them a pituitary adenoma It is interesting to speculate if the hyperprolactinemia could be a result of the treatment with contraceptive pills conflicting results have been presented in the literature (for references see 1) However among our cases of spontaneous amenorrhea 9 patients with longstanding amenorrhea (>3 years) associated with hyperprolactinemia and 3 of them had a pituitary adenoma Furthermore there were no differences in the gonadotrophin and estrogen levels between the two groups This speaks in favour of other factors than oral contraceptives as a cause of the hormonal disturbance

All patients who were treated with bromocriptine started to menstruate and all of them who wanted became pregnant It is well known that when treatment with bromocriptine is stopped the high secretion of prolactin and the amenorrhea return The question arises if patients who do not want to become pregnant have to be treated If they start to menstruate they have of course to use some kind of contraception Provided the patients are checked regularly for a possible pituitary adenoma it may be better to substitute the lack of ovarian hormone with genuine estrogens and progesterone This treatment on the other hand is not without risk as it is known that pituitary tumors grow under the influence of estrogens Among our patients 2 wanted to stop bromocriptine treatment and have substitution therapy instead

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ANNOUNCEMENT

The VIth International Congress of Psychosomatic Obstetrics and Gynecology will take place in West Berlin September 2–6 1980 The principle theme of the Congress — *Women in a changing society* — *is meant to encourage lectures and discussions dealing with socio-psychological characteristics and cultural influences psychosomatic symptoms* and illness as well as with the psychotherapeutic potential in obstetrics and gynecology

The Congress program includes plenary lectures delivered by invited speakers as well as short lectures on recent psychosomatic findings In additon to those working groups scientific films and demonstrations are being planned

Languages of the Congress
English French Spanish and German

Information may be received from
Scientific Secretariat
Ass Prof Dr M Stauber
Frauenklinik Charlottenburg der FUB
Pulsstrasse 4
D 1000 Berlin (West) 19
West Germany

Organizational Secretariat
W Syborg (COG)
John Foster Dulles-Allee 10
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West Germany

An International Symposium on **Carcinoma of the [illegible]** will be held on Kiawah Island Charleston South Ca[illegible] USA September 4-7 1980

Program Committee
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Medical Research Building
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For information telephone Jane Wittersheim at (313) 494-7286

The First International Symposium on Recent Prenatal Diagnosos will be held at the *Pa[illegible] e Dei Congressi* in Bologna Italy on the 15th [illegible] September 1980 The symposium organized by the [illegible]rical and Gynecological Department of the Bologna [illegible]sity and by the F Angelini Research Institute [illegible] include a number of Round Tables on prenatal diagnosis

Presidents of the Congress are
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AN ANALYSIS OF THE INTENSITY AND QUALITY OF GYNECOLOGICAL PAIN

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ct It is evident that the pain experience varies
tively as well as in intensity A number of methods to
both the intensity and quality of pain have been
d This paper presents the results of a card sort
l of pain assessment in the measurement of gyne
al pain which provides a score from 1 to 4 for 10
ialities Factor analysis has identified 3 main clusters
i dimensions sensations reaction and a timing/dura
mension
iparative data is presented on 5 main pain types using
ethod dysmenorrhea IUD related pain IUD inser
in postoperative pain and post partum pain A total
patients were assessed The results permit compari
etween pain types for both intensity as well as quality
istinction may have implications for pain manage
Thus although dysmenorrhea and IUD related pain
milar in terms of sensations dysmenorrhea was rated
cantly higher in terms of the reaction component
rly both IUD insertion pain and post partum pain
d high reaction scores The implications of such a
profile are discussed Thus these scores may result
the unexpected nature of the pain sensations rather
their high intensity In which case inclusion of
ological preparation may have been of benefit
rly with pelvic pain of unknown organic origin sub-
il relief may be provided by focussing on the reaction
nent where this is elevated and removing the worry
nding the sensations

without identifiable organic cause is a common
nting complaint in gynecological clinics As
p (9) comments pain occurring below the um
s in the female abdomen is probably one of the
common presenting symptoms in gynecology
ask of the gynecologist is both the diagnosis so
treatable organic pathology is excluded and ef
e management of the pain In order to ac
lish this suitable methods of pain assessment
be available as it is necessary to rely upon the
nt s verbal description of pain for both diagnosis
subsequent evaluation of treatment response It
dent that pain varies qualitatively as well as in in
ty (variation which needs to be reflected in pain
ures so that changes in either intensity or quality
s time are apparent) Thus Beecher (3) stressed
that the pain experience is dependent upon both the original sensations and the psychic processing of this sensation i e the reaction or evaluative component of pain The way in which psychological processes such as mood personality and culture can affect the reaction to similar sensations is well documented (20) Attempts to measure pain should take account of this evidence as information will be lost by relying on rating scales which treat pain as a single sensory quality varying only in intensity

In view of the need to measure the quality as well as intensity of pain over time a number of multidimensional assessment techniques have been described Melzack (11) presented a questionnaire which provides scores on three main dimensions sensory affective and evaluative Alternatively combinations of rating scales have been used to independently assess the sensory and distress/reaction components of pain (8 10) A card sort method which provides a range of scores from 1 to 4 for 10 pain qualities has also been described (19) An evaluation of this method found it to have high reliability and concurrent validity in that sort scores were closely related to other pain indices such as taking pain killers going to bed etc (18)

This paper presents the results of the routine use of this card sort method in in patient and out patient gynecological settings Information on intensity ratings for a range of pain qualities will be presented for 5 types of pelvic pain dysmenorrhea intrauterine device related pain post IUD insertion pain postoperative pain and postpartum pain The aim in supplying this information is to aid the physician in his understanding of patient s pain complaints

MATERIAL AND METHODS

Over the course of an 18 month period a total of 232 patients have been seen for a pain assessment The card sort is in the form of paired comparisons There are 10 qualities or triads each consisting of three words reflecting different amounts of qualitatively similar pain experience (Table I) For example the words pulsing throbbing pounding refer

Table I *Pain card sort assessment content*

	Intensity		
Triad number	i	ii	iii
1	pulsing	throbbing	pounding
2	dull	aching	heavy
3	pulling	cramping	wrenching
4	pricking	boring	stabbing
5	nagging	sickening	agonising
6	slightly tiring	tiring	exhausting
7	brief	every now and then	constant
8	annoying	miserable	unbearable
9	mild	discomforting	excruciating
10	slightly distressing	distressing	very distressing

Table II *Mean age according to pain group*

Pain group	Mean age	No
Dysmenorrhea	24 4 (8 0)	102
IUD related pain	24 2 (5 3)	38
Post insertion	23 7 (5 4)	22
Postoperative	30 3 (4 9)	55
Postpartum	24 0 (8 4)	15

Standard deviations in brackets

to different amounts of a similar pain sensation and represent one of the 10 triads The content of the test was drawn from a survey of over 200 women complaining of pelvic pain (16) Only words within a triad are compared which means as there are 3 cards for each triad there are 30 cards in the present form of the test The method of paired comparisons permits the internal consistency of each administration to be established

RESULTS

The number of patients in each of the pain shown in Table II along with their mean age R are presented for Caucasian patients only as th sent form of the card sort was developed for use this ethnic group and may not be directly app to others in view of the documented variation of pain descriptors across ethnic groups (7)

In Table III a distinction is made between ca scores of 1 and 2 (minimal and mild) and 3 (moderate and severe) and the percentage of p within each pain group achieving these score ented Chi Square analyses of associations b scores and pain types for each pain triad w

Table III *Percentage of patients scoring high (3 4) or low (1 2) on each triad of the card sort according group*

Triad number	Score	Dysmenorrhea (%)	Pain IUD related (%)	Postinsertion (%)	Postoperative (%)	Post partum (%)	Significance of χ^2
1	low	53	55	83	45	67	
	high	47	45	17	35	33	$p < 05$
2	low	54	61	55	61	78	
	high	48	39	45	39	22	NS
3	low	71	68	77	82	56	
	high	29	32	23	18	44	NS
4	low	33	29	46	53	45	
	high	67	71	54	47	55	NS
5	low	64	88	65	87	67	
	high	38	12	35	11	32	$p < 01$
6	low	48	84	73	80	56	
	high	52	16	27	20	44	$p < 01$
7	low	36	54	51	41	66	
	high	64	46	49	59	46	NS
8	low	62	79	74	95	67	
	high	38	21	26	5	33	$p < 01$
9	low	47	66	59	88	45	
	high	53	36	41	12	55	$p < 01$
10	low	60	79	69	95	56	
	high	40	35	31	5	44	$p < 01$

e IV *Mean total and factor scores on card sort according to pain group*

group	No	Card sort total	Sensation factor score	Tiring/temporal factor score	Evaluative factor score
ıenorrhea	102	25 2 (6 9)	7 3 (2 2)	5 5 (1 7)	9 8 (3 8)
related pain	38	22 0 (6 4)	7 6 (2 3)	4 4 (2 3)	7 3 (3 6)
insertion	22	22 0 (6 3)	6 1 (2 1)	4 6 (1 4)	8 2 (3 7)
operative	55	19 6 (6 2)	5 8 (2 9)	4 4 (2 2)	5 8 (2 6)
partum	15	21 5 (7 4)	7 1 (2 3)	5 0 (1 6)	9 3 (1 5)

dard deviation in brackets

ficant associations for triad 5 ($\chi^2 = 15\ 8$ df=4 01) triad 6 ($\chi^2 = 21\ 2$ df=4 $p < 01$) triad 8 =24 3 df=4 $p < 01$) triad 9 ($\chi^2 = 27\ 9$ df=4 01) and triad 10 ($\chi^2 = 24\ 0$ df=4 $p < 01$) With exception of triad 1 ($\chi^2 = 12\ 2$ df=4 $p < 05$) ificant associations between pain quality and pa group are found for triads describing the nomic and evaluative nature of the pain Less ation between groups is found for sensation ls

ean summated card sort scores and factor scores calculated and are shown in Table IV Factor ysis showed a priori clusters of triads to be con ed with three main factors emerging (18) These ted to sensations (triads 1 3 and 4) the evalua of the pain (triads 5 8 9 and 10) and a third fac elating to the tiring/temporal dimension (triads 6 7) Associations between mean card sort totals mean scores on each factor were assessed by anal of variance It was found that total card sort was significantly associated with pain type 5 4 df=4 $p < 01$) Similarly factor scores were significantly related to type of pain sensation 4 9 df=4 $p < 01$) tiring/temporal (F=4 6 4 $p < 01$) and evaluative (F=10 0 df=4 01)

he significance of paired comparisons between ps were assessed by double tailed t tests in r to identify the source of this significant be n group variation It can be seen from Table IV dysmenorrhea was assigned the highest score all This was significantly higher than the totals the other pain groups (Dysmenorrhea and IUD ed pain $p < 01$ Dysmenorrhea and postinsertion $p < 05$ Dysmenorrhea and postoperative pain 001 Dysmenorrhea and postpartum pain 05)

he significance of factor score differences be n pain grouips was also assessed Comparison of nenorrhea with IUD related pain showed signifi cantly higher scores on the evaluative ($p < 01$) and tiring/temporal ($p < 001$) components for the dys menorrhea group Sensory factor scores were similar for both groups Dysmenorrhea was reported to be significantly more painful than postinsertion pain in terms of both sensations ($p < 05$) and tiring/tem poral quality ($p < 05$) although the evaluative score did not differ significantly In comparison with post operative pain dysmenorrhea was rated as signifi cantly more severe on all three components sensation ($p < 001$) tiring/temporal ($p < 001$) and evaluative ($p < 001$) No significant differences between dysmenorrhea and postpartum pain emerged

A comparison of IUD related pain with post IUD insertion pain showed higher sensation ratings for IUD related pain ($p < 05$) with no significant dif ference in terms of either tiring/temporal or evalua tive dimensions IUD related pain was reported to be significantly more painful in terms of both sensations ($p < 01$) and evaluation ($p < 01$) than postoperative pain No significant differences between IUD related and postpartum pain occurred

Post insertion pain was rated as significantly more severe than postoperative pain in terms of evaluation ($p < 01$) Differences between post insertion and postpartum pain failed to reach significance Post partum pain was rated as significantly more severe in terms of evaluation ($p < 001$) compared to post operative pain

A discriminant function analysis was carried out in the attempt to distinguish between the 5 pain groups on the basis of their score profiles This classification method is designed to maximise the discrimination amongst groups defined a priori (15) The posterior probability of group membership (the probability of a patient belonging to each pain group conditional on their card sort scores) was determined from the discriminant functions and their prior probabilities (conditional only on the respective sample sizes) of group membership According to these measures

Table V *Evaluations of individual cases based on proximity to closest group centroid*

Original pain group	Dysmenorrhea	IUD related pain	Post insertion pain	Postoperative pain	Postpartum pain
Dysmenorrhea	35	20	12	23	12
IUD related pain	2	19	4	7	6
Postinsertion pain	4	4	9	3	2
Postoperative pain	4	11	4	36	0
Postpartum pain	1	1	1	1	5

Figures shown are number of cases classified

every case was evaluated to determine how closely each patient s description of her pain as revealed by distribution of scores on the card sort resembled the average description by all patients with the same diagnosis It was found that 42 per cent of all patients in the study resembled those of their own pain type more than any other and were thus correctly classified by the analysis (Table V)

Finally Pearson product moment correlations between factor scores and card sort totals were computed The correlation matrix is shown in Table VI It can be seen that all correlations are significant although not sufficiently high to indicate overlap and therefore duplicity

DISCUSSION

This paper presents a comparison in terms of both intensity and quality of common gynecology pains The assessment method employed was found to have sufficiently high reliability and validity to justify such a detailed analysis (18) The multidimensional nature of this assessment allows the pattern of the pain response for each patient group to be described This is felt to be important in term of implications for pain management For example Weisenberg (20) stressed the importance of psychological variables in the pain experience so that even where pharmacological means are used to control pain the psychol status of the patient often determines their che effectiveness Beecher (4) has cited many instan this for example the greater the stress the mor fective the placebo An analysis of the pain m of its various components may clarify treatmen jectives Thus the patient with low sensation sc and high evaluation may respond to reass and/or relaxation training without the need analgesics

Analysis of pain descriptions have been rep elsewhere (1 5 11 12) Melzack and Dubuiss analysed the descriptions used according to ? types (menstrual toothache cancer arthritis herpes phantom disc disease) They were ab correctly classify 76 per cent of the 95 patients sample to the correct pain group on the basis of questionnaire scores

In the present study discriminant function a revealed a correct classification rate of less th per cent This was significant although not cle useful in terms of predicting pain type from car scores However the result should be seen in the text that the pain groups in this study wer varieties of pelvic pain as compared with the M and Dubuisson (6) study in which a wide rang pains were investigated The widest difference study was between dysmenorrhea and posto

Table VI *Correlation coefficients between card sort total and factor scores*

	Sensory factor score	Tiring/temporal factor score	Evaluation factor score	Total
Sensory factor score		399	529	711
Tiring/temporal factor score			549	669
Evaluation factor score				884

All correlations significant at $p > 001$ level

n When these two were compared by discriminant ction analysis the correct classification rate in ised to 70 per cent

n terms of intensity comparisons dysmenorrhea ieved consistently higher scores than other pain s Interestingly while no difference in sensations evident between dysmenorrhea and IUD related significant differences in terms of reaction to e similar levels of sensation did emerge This cor nds to the results of an early survey (16) in no difference in sensation was found It also rms to predictions in that IUD relation pain ions may be better tolerated (give rise to less ss) owing to the cause of the pain (the IUD) be early identified Moreover women experiencing elated pain have chosen this method of contra i and the pain arising from the IUD can be off gainst the positive benefits of contraceptive The opposite is the case with dysmenorrhea as are no positive aspects to diminish the signifi of the pain

smenorrhea was rated as giving rise to signifi greater pain on all dimensions This is also in d with predictions as the postoperative pain d was related to a relatively minor gynecologic ration (laparoscopy) which had been elected by tient and for which the prognoses were favor Sensations have been found to be better ited if the perceived cause has been voluntarily ted by the sufferer as in the case of postopera ain and IUD related pain (2)

ile the degree of sensation did not differ be IUD related pain and post insertion pain the ficance or reaction attached to these sensations greater following the IUD insertion Evidence sts IUD insertion will be rated as less painful if nts are adequately prepared (17 14) This finds ect support from the present data as the reac component was higher for post insertion pain ating the possibility that patients were insuffi ly prepared for the sensations to be experienced igh levels of postpartum pain were reported in s of both sensations and the reaction to these ations Once again it may have been expected pain following delivery would have been well ated owing to its associations with a positive ex nce that of childbirth as the meaning of the tion in which the pain occurs has been shown to t its intensity (3) Thus increased pain reports at ery have been associated with ambivalent feel about the prospect of motherhood (13) The present results may have two implications In the first place the high intensity of the pain sensations is noteworthy Secondly the high reaction shown by patients in the present study may be the result of a lack of preparation for the possibility of such pain occurring In the absence of such information the experience of pain may be associated with anxiety about possible complications and so be invested with undue significance It would be predicted that inclusion of psychological preparation would have the effect of reducing the evaluative component of the pain

In conclusion it appears that this method of pain assessment provides a meaningful way of describing gynecological pain This survey has provided normative data on the severity of different pelvic pains in terms of quality as well as intensity and so permits comparisons of one with another It also allows the clinician to compare individual patient scores with the average of the appropriate reference group The profile of pain which emerges may have implications for management For example both post insertion and post partum pain may be relieved by prior information and reassurance in order to reduce the significance that is attached to the sensations arising from each of these experiences The profile of pain scores may also influence treatment of dysmenorrhea or pelvic pain of longstanding In the course of running a pain clinic it has become evident that many patients are concerned by the significance of their pain experience which is reflected in high evaluative scores It follows that substantial reflief may be provided by focussing on the elevated reaction component of the pain and removing the worry surrounding the sensations

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PHARMACOKINETIC STUDIES ON LOW DOSE ESTRADIOL 17β ADMINISTERED ORALLY TO POSTMENOPAUSAL WOMEN

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...ract Peripheral plasma from four postmenopausal ...en was analysed for estrone estradiol luteinizing hor... and follicle stimulating hormone during 24 hours ...wing an oral intake of a single dose of 1 0 mg microniz... ...tradiol on the first day of therapy and after one ...h A similar study was carried out with another four ...nenopausal patients who received 0 2 mg estradiol ... times daily The measurements were performed by ...immunoassay (RIA)

...s concluded that the plasma concentrations of estrone ...stradiol are higher and those of FSH lower after one ...h of therapy than on the first treatment day while ... a LH remains unchanged Micronized estradiol is ...y absorbed from the gastrointestinal tract and con... ...l to estrone and the plasma profiles of estrone during ...ly are more constant with a divided daily dose than ...a single higher dose The divided daily dose results in ...ually good clinical effect even though the total ad... ...ration of estradiol is lower

...posed estrogen therapy for menopausal symp... seems to be associated with an increased risk of ...netrial cancer (5) Even though this risk may be ...ized by giving an adequate cyclic progestin ...ent with the estrogen therapy an unnecessari... ...h daily dose of estrogen is still a cause of con... This makes it important to establish the lowest ...ive daily dose of estrogen The aim of the pre... ...study was to determine the effect of reducing ...ily amount of estrogen and dividing it into three

The metabolism and pharmacokinetics of ...nized estradiol were studied at the beginning of ...py and again after one month s treatment

MATERIAL AND METHODS

...healthy postmenopausal women participated in the ... The last menstrual period in each of these subjects ...t one had occurred more than one year but less than ...ears before the study The exception had a menopause ...age of 34 19 years before entering the study Every ...it had severe symptoms of vasomotor instability and ...ot used any hormonal medication for one month be... ...he study The results of the vaginal smears of each subject were menopausal and atrophic The breasts were studied by mammography and thermography and were considered to be normal The subjects were randomly selected into two groups for treatment The first group received tablets containing one milligram of micronized estradiol at 8 a m every day The second group took a tablet containing 0 2 mg of micronized estradiol at 8 a m 2 p m and 8 p m The micronization of steroid and the quality of the tablet were the same The tablets were specially prepared by Novo Industry A/S Copenhagen Denmark for this trial The absorption and effects of the drug were followed by collecting blood samples for the determination of plasma concentrations of estrone (E_1) estradiol (E_2) follicle stimulating hormone (FSH) and luteinizing hormone (LH) by radioimmunoassay (RIA) Blood samples were collected during the first day of treatment before the first intake and 1/2 1 1 1/2 2 3 5 7 9 12 and 24 hours after the ingestion of the tablet in the group receiving one milligram of E_2 In the second group the samples were collected on the morning before the intake of the tablet and then 1/2 1 2 3 and 5 hours after the ingestion of each of the three tablets Indentical collections were performed after one month of treatment The blood was collected into heparinized tubes plasma was separated by centrifugation and stored at −20 C until analyzed All samples were analyzed simultaneously

E_1 and E_2 were measured by RIA after diethylether extraction without chromatography as described by Edqvist & Johansson (3) The cross reaction of E_1 in the E_2 RIA was 1 24 per cent and that of E in the E_2 RIA 1 65 per cent The intra assay coefficient of variation (C V) for E_1 varied from 5 3 to 9 3 per cent and for E_2 from 7 7 to 9 0 per cent The interassay C V for E_1 RIA varied from 16 0 to 18 9 per cent and for E_2 from 9 3 to 10 5 per cent

The RIA s of plasma FSH and LH were carried out as described earlier (7) The intra assay C V was 9 3 and 2 4 per cent for FSH and LH respectively The interassay C V was 14 7 per cent for FSH and 14 2 per cent for LH

The evaluation of clinical effects involved comparing the frequencies of neurovegetative symptoms estimated subjectively by the patient before and after treatment (4 9)

RESULTS

The clinical effect of the treatment as evaluated by the patients was the same in both groups (Table I) There was one failure in both groups The patient in the first group had persistently high gonadotropins

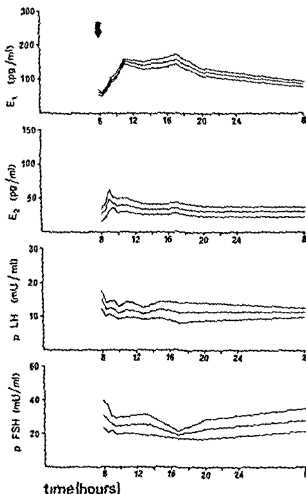


Fig 1 Plasma concentrations of E_1, E_2, LH and FSH after ingestion of 1 0 mg micronized E_2 at 8 a m mean and SE curves during one day The arrow(s) indicate ingestion of the tablet(s)

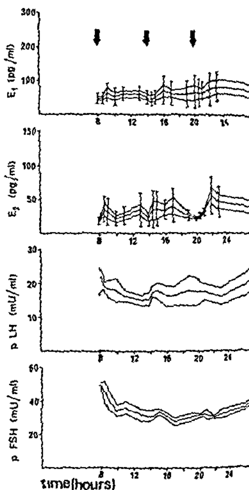


Fig 2 Plasma concentrations of E_1, E_2, LH and F ingestion of 0 2 mg micronized E_2 at 8 a m ? p m mean and SE curves during one day For E ; SD also shown as vertical lines The arrow(s) indica tion of the tablet(s)

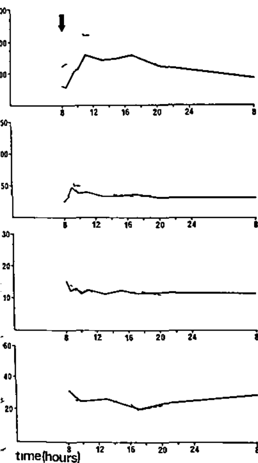
and the patient in the second group had no change in plasma E_2, E_1, LH and FSH concentrations

Table II gives the plasma concentrations of estrogens and gonadotropins at 8 a m before and after the treatment for one month The basal values of estrogens were higher and gonadotropins lower in group I than in group II After treatment for one month the mean morning levels of plasma estrone and estradiol were increased the plasma concentrations of LH were unchanged but FSH decreased The change during treatment expressed as a percentage of the pretreatment values was very similar in the two groups except for plasma e tradiol which was relatively more elevated in group II where the treatment consisted of three doses a day

The mean plasma concentrations of E_1, E and FSH during the first 24 hours after the ... mg of E_2 are presented in Fig 1 The plasma E centrations increased during the first three from 62 to 156 pg/ml and are clearly elev hours after drug intake There was also a secon 9 hours after the administration of E_2

Plasma E_2 reached a minor peak after one and tended to plateau five hours after the E - The LH plasma levels decreased during the fo hours and remained at this level during the o tion period Plasma FSH concentrations first de ed rapidly reached a nadir at the time of th s estrone peak and increased slowly after that

The average plasma concentrations of prol



Plasma concentrations of E_1 E_2 LH and FSH after ingestion of 1 0 mg micronized E_2 at 8 a m Continuous line shows the mean plasma concentrations on the first treatment day (like in Fig 1) the broken line shows the mean plasma concentrations after one month s therapy The arrow(s) indicate ingestion of the tablet(s)

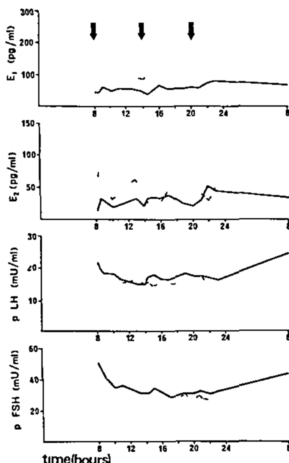


Fig 4 Plasma concentrations of E_1 E_2 LH and FSH after ingestion of 0 2 mg micronized E_2 at 8 a m 2 p m and 8 p m Continuous line shows the mean plasma concentrations on the first treatment day (like in Fig 2) the broken line shows the mean plasma concentrations after one month s therapy The arrow(s) indicate ingestion of the tablet(s)

LH and FSH during the first day after three doses of 0 2 mg of estradiol are shown in Fig 2 Plasma concentrations of estrone increased slowly until the last sample on the first day Small peaks one to three hours after the administration of the drug could be seen Plasma estradiol increased slightly after each administration and a cumulative effect was seen at 10 p m when the mean level reached 55 pg/ml Plasma LH was suppressed during the day but the 24-hour value reached the basal level The suppression of plasma FSH was slightly stronger than that of LH

The mean plasma concentrations of E_1 E_2 and LH for group I are given in Fig 3 and those of group II in Fig 4 for samples taken during the first treatment day and the day after one month of treatment The mean plasma concentrations of estrone in women taking 1 mg of E_2 were higher after one month of treatment than during the first treatment day (Fig 3) The peak value was reached sooner but the plateau decreased at the same time as in the beginning of the trial i e nine hours after the ingestion of one milligram of E_2 The mean concentration curve of plasma E_2 during the day after one month of treatment was very similar to that obtained on the first treatment day The decreases in plasma LH and FSH resembled those seen during the first day

As shown in Fig 4 the mean plasma estrone concentration was quite stable during the whole observation period The mean level was however signifi

Table I *Clinical effect of the treatment Patient s subjective evaluation after one month Group I received 1 0 mg of E_2 daily group II 0 2 mg of E_2 three times daily*

Effect	Group I	Group II
Very good	2/4	2/4
Good	1/4	1/4
Poor	1/4	1/4

cantly higher after one month of treatment than during the first day and was about 100 pg/ml throughout the day Plasma estradiol levels were also significantly higher after one month of therapy than during the first day of treatment There were also peaks preceding the intake of the second and third doses The gonadotropins were suppressed during the day time but in group II the suppression was not as clear as at the beginning of the treatment because the morning value of FSH was low

DISCUSSION

The results of the present study show that there are no significant differences in the morning plasma concentrations of E_1 E LH and FSH after one month of treatment when E_2 is given as a single dose of 1 0 mg or as 0 6 mg divided into three doses Therefore it seems that the daily dose of estradiol can be successfully reduced by dividing it into three doses The divided administration also gave a more constant plasma level of E_1 than a single daily dose and the high concentrations associated with higher doses were eliminated

The oral administration of estradiol resulted in higher plasma concentrations of E_1 than E_2 as shown before with micronized estradiol by Yen *et al* (10) and with estradiol valerianate by Englund & Johansson (4) and Larsson Cohn *et al* (8) It seems that there is no difference in the relative plasma levels of E_1 and E_2 when the patients are treated with es[illegible] iol valerianate or piperazine estrone sulphate (1)

The plasma concentrations of E_1 and E[illegible] higher after one month of treatment than during [illegible] first day This could reflect a saturation of the [illegible] ous pools An alternative explanation could be [illegible] estradiol has a local effect on the intestinal m[illegible] which could increase absorption There wa[illegible] tively higher increase in plasma estrone [illegible] during the day of administration compared [illegible] of estradiol after one month of treatment T[illegible] suggest an adaptation of the enzyme respons[illegible] the conversion of estradiol to estrone In this [illegible] vasomotor symptoms disappeared in all the [illegible] who reacted to the treatment with elevated es[illegible] levels and decreased gonadotropin concentra[illegible] This is in sharp contrast with the results of H[illegible] *al* (6) who found no relation between the tim[illegible] flush and estrogen concentrations Howeve[illegible] conclusion was based on fluctuations of low p[illegible] concentrations of estrogens without any treatm[illegible]

A constant plasma concentration could perha[illegible] achieved with peroral medication by changing th[illegible] cronization size of the tablets or even using s[illegible] lease capsules to avoid dividing the daily dose [illegible] beneficial for the treatment

In conclusion rapidly absorbed microniz[illegible] iol results in a good therapeutic effect by p[illegible] ministration and stable plasma concentratio[illegible] achieved even with a lower total dose by div[illegible] daily dose

ACKNOWLEDGEMENTS

This study was supported by Novo Industry A/S [illegible] gen Denmark The National Pituitary Agency [illegible] tional Institute of Arthritis Metabolism and [illegible] Diseases is gratefully thanked for supplying [illegible] FSH and the antisera for these radioimmunoassay[illegible] also to Dr J P Raynaud for supplying the [illegible] steroid assays

Table II *Mean plasma concentrations ±SEM of E_1 E_2 FSH and LH at 8 a m in the two groups bef[illegible] after one month of therapy with estradiol Change from the pretreatment value is given in per cent E_1 pg/ml LH and FSH IU/l*

	Group I (n = 4)			Group II (n = 4)		
	before	after	change (%)	before	after	change (%)
E1 (pg/ml)	63 1±9 3	125 0±20 0	+98 1	39 9±4 3	84 0±21 2	+110 5
E2 (pg/ml)	26 3±7 1	38 0±10 0	+44 5	17 3±3 4	31 5±4 7	+82 1
LH (IU/l)	15 0±1 6	14 4±3 8	−4 0	21 9±2 4	20 7±2 6	−5 5
FSH (IU/l)	31 7±5 1	24 1±5 7	−24 0	46 8±1 4	35 6±1 8	−24 4

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ANNOUNCEMENT

The Pan American Congress of Andrology will take place in Mexico City Americana Fiesta Palace Hotel January 26–31 1981

Informations requests for registration and travel information should be directed to

Dr A Negro-Vilar
University of Texas Health Science
Center at Dallas
Southwestern Medical School
Department of Physiology
5323 Harry Hines Boulevard
Dallas Texas 75235
USA

Informations requests for registration and travel information should be directed to

Gerald Bagazinski
Congress Administrator
31600 West Chicago
Livonia Michigan 48150
USA

The Third International Congress on the Menopause held in Belgium at the coastal resort of Ostend 9–12 1981 just before the holiday season begins

This Congress will differ from the previous two Grande Motte 1976 and in Jerusalem 1978) in that as the aim in the past was to arrive at a consensus of ion this time we shall bravely attempt to confront troversies It will however take the same form as the ones — a number of small workshops rather than a meeting attended by everyone

For further information

The International Menopause Society
8 av Don Bosco
B 1150 Brussels
Belgium
Tel (02) 771 95 98 and (02) 771 96 45

The IIIrd World Congress of Human Reproduction is to be held in West Berlin March 22 26 1981

Main topics

Central nervous system and regulation of reproduction

- Surgical and morphological aspects of reproduction in men and women
- Gonadotrophins and their target tissue
- Beginning of life *in vivo* and *in vitro*
- Experimental embryology of mammals
- High risk reproductive factors in breast and genital cancer
- Influence of the environment and drugs on reproduction

Free Communications

- Film Festival

Information

Congress Secretariat
Priv Doz Dr L Mettler
Frauenklinik der Universität
Hegewischstrasse 4
D 2300 Kiel 1
West Germany

The Eight Asian Congress of Obstetrics and will be held in Melbourne in October 1981

An exciting and varied programme will be cluding expert plenary speakers from Asia other Centres The Congress themes include

- Population Control

Maternal and Perinatal Mortality

- Trophoblastic Disease

Gynaecological Malignancy

- Obstetrical and Gynaecological Endocrinology

The official language will be English

Further information may be received from

The Organizing Secretary
VIIIth Asian Congress of
Obstetrics and Gynaecology
G P O Box 2195T
Melbourne 3001
Victoria
Australia

DO ESTROGEN AND PROGESTERONE RECEPTORS (E_2R AND PR) IN METASTASIZING ENDOMETRIAL CANCERS PREDICT THE RESPONSE TO GESTAGEN THERAPY?

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stract In a prospective investigation biopsy specimens obtained of 150 women with primary untreated endo- nal carcinoma for determination of the content of estro- and progesterone receptors (E_2 and PR) After a vary interval 13 who developed metastases despite routine ical and radiation therapy received treatment with ges ns The clinical effect of the hormone was studied for correlation with the initial content of E_2 and PR ght of the women (61–71 years) proved E_2R positive 0 fmoles/mg cytosolprotein) 2 had no PR and the re ing 6 had PR in a concentration of 7–892 fmoles/mg solprotein) 7 responded clinically to gestagen therapy iors poorly differentiated in 3 and moderately in 4) ve of the women (50–84 years) were E_2R negative they no PR they did not respond to gestagen therapy and di fter 2–8 months (tumors poorly differentiated in 2 and erately in 3)

termination of E_2R and PR in endometrial carcinoma ears to be a clinically useful test for predicting whether a ent is likely to respond to treatment with gestagens

mor therapy with progestagens can produce a ificant regression in about one third of all cases of anced or recurent endometrial carcinoma The age duration of the remission achieved by ges n therapy alone in these cases of hormone -de dent adenocarcinomas is 14 months and the aver duration of survival 2–3 years (21) The pro- sis is usally best if the tumor is highly differen ed and the metastases are confined to the lungs response is also said to be better if the woman is ing (15) However excellent results have been ob- ted with low dosage progestagen therapy even in s where the prognosis was initally very gloomy) Estrogenic vaginal smears may be another sign tumor responsiveness to gestagen therapy while ther the level of estrone nor of estradiol in serum ms to be of any prognostic value (2)

rogesterone seems to exert its effect locally on the ls of endometrial carcinoma leading to differentiation maturation and secretion and finally atrophy of the tumor epithelium Evidence in support of this view has been produced by Nordqvist (18) and others

It is claimed that the presence of specific cyto- plasmic progesterone receptor protein (PR) is neces sary for progesterone to exert its cellular effect Such receptors are generally demonstrable in normal endo- metrium but may also be found in endometrial carci noma PR activity is less if the tumor is poorly differ entiated Thus in 23 cases examined Ehrlich *et al* (3) found a high PR content (>50 fmol/mg cytosolpro- tein) in 85 per cent of highly differentiated cases in 62 5 per cent of moderately differentiated ones and in only 50 per cent of undifferentiated tumors Ir respective of the degree of differentiation tumors that had previously been irradiated showed no evidence of PR The PR content has also been found to vary in versely with the patient s age (22) The difference in PR content between highly and poorly differentiated endometrial cancer has also been demonstrated by Pollow *et al* (19) who in 15 cases examined found low concentrations of PR within a narrow range of 3–63 fmol/mg cytosolprotein In a later series of 30 cases Pollow *et al* (2) found the highest E_2R content in those tumors that had a low PR content and that were undifferentiated In contrast in a recent study of 50 primarily untreated cases of endometrial carcinoma Friberg *et al* (6) found that E_2R was most often demonstrable in differentiated carcinoma which also most often had receptors for androgen (DHT) Specific DHT receptors have been demonstrated recently in normal human endometrium (17) Of 11 patients with endometrial carcinoma Gustafsson *et al* found PR in nine the content generally being lower in those cases where the tumor was poorly dif ferentiated Normal endometrium contained about 400 fmoles/mg protein while endometrial carcinoma contained 0–62 fmoles/mg

Table I *E_2R negative metastasizing endometrial cancers treated with gestagens Clinical data*

Patient age	Tumor grade of differentiation	Metastatic spread to	Gestagen treatment and survival time
67	low	pulm pelvic tissues	500 mg Proluton Depot 5 times weekly Progress 4 months
74	medium	omentum pelvic tissues	500 mg Proluton Depot 5 times weekly Progress 8 months
77	medium	pulm	50 mg Depot Provera weekly Progress 3 months
50	medium	pulm skeleton	500 mg Proluton Depot 3 times weekly Progress with neo pulm met 3 months
84	low	pulm	500 mg Proluton Depot 3 times weekly No effect but progress 2 months

The purpose of the present investigation was to find out whether the in vivo results of progesterone treatment of recurrences and metastases from endometrial carcinoma treated with surgery and radiation was correlated with the in vitro occurrence of E_2R and PR *in the primary untreated tumor tissue*

MATERIAL AND METHODS

The material consisted of biopsy specimens of the endometrium obtained at diagnostic curettage of women with untreated primary endometrial carcinoma Part of the tissue was fixed in formalin for routine histological examination and grading Highly differentiated tumors showed glandular tubules with cylindrical epithelium while poorly differentiated tumors exhibited solid cellular areas or solid cords with epithelial cells Moderately differentiated tumors showed a picture intermediate those of the other 2 Small pieces of tumors were also transferred to glass tubes immediately deep-frozen and stored until receptor analysis Of the 150 patients from whom such specimens were obtained in the course of a 3 year period there were 13 who despite routine surgical and radiation treatment had a local recurrence or developed remote metastases which were then treated with gestagens Pieces of the primary tumors from these 13 women were analysed for their content of estrogen (E_2R) and progesterone (PR) receptros The values found were studied for any correlation with the clinical effect of the hormone therapy

The stored tissue was transferred into liquid nitrogen and vibrated to a fine powder by means of a microdismembrator The powder was homogenized in cold buffer using a Ten Broeck homogenizer and centrifuged at 105 000 g for 60 min to prepare the cytosol The cytosol was analysed for estradiol and progesterone receptor activity as published (1) In brief 50 μl cytosol samples were transferred into the holes of microtiterplates and incubated with six different concentrations or ^3H E_2 or ^3H R 5020 The nonspecific binding for ^3H E_2 *and* ^3H *R 5020 was determined in the* presence of a large excess (1 μM) of nonradioactive R 5020 and DES respectively

After equilibrium was reached (16–20 hr at 4 C) the bound steroid was removed by the addition of 10 dextran coated charcoal suspension Scatchard plot ana-sis was performed to determine the concentration of tor binding sites and the equilibrium dissociation cons (K_d)

RESULTS

To discriminate for the presence of estrogen receptors in our endometrial cancer patients values ≥10 fmoles/mg protein were reported as pos This cut off level for E_2R has previously been ap in the study of estrogen binding capacity of p- mary cancers Clinical details of 5 such E R neg patients and the histopathology of their tumors shown in Table I None of the E_2R negative pati shown in Table I had any PR content in the pri tumor material analysed In spite of gestagen tr ment their survival was short between 2–8 mon without any certain relation to age or histopathol of the tumor

Table II shows the clinical details and the h pathology of the tumors of 8 cases who were all positive With the exception of 2 cases they al *had PR 7 cases responded well to* gestagen ther with survival time of those who are dead of 6 1 and 20 months 3 are still living symptom free

DISCUSSION

The possible importance of the presence of hor receptors in endometrial carcinoma if gestagen th- py is to check spread of the tumor has so far b studied in only a few cases The presence of rec need not however mean that the tumor is respo to hormone therapy since there may be a defic

Table II. *Data on age of patient, histological grade of tumor differentiation, amount of E_2R and PR (fmol/mg protein), metastatic spread and the effect of gestagen treatment*

	Grade	E_2R	PR	Metastatic spread	Gestagen treatment and survival time
	low	2..	43	pelv c tis ues ag na	1000 mg Depot Pro era weekly Progress 3 months
	low	133	89	skeleton	500 mg Proluton Depot 3 times weekly Impro ed Died of pulm embolia after 6 months
	medi m	37	7	supraclav and inguinal lymph nodes	500 mg Depot Provera weekly Impro ed with regression fo 3 months then progress 11 months
	medium	64	16	pulm	1 000 mg Depot Provera weekly Metastases reg essed for 9 months then progress 18 months
	low	22	0	pulm vagina pel ic tissue	1 000 mg Depot Provera weekly Regression for 8 months then progress 20 months
	medi m	70	72	pelvic tissues ag na	500 mg Proluton Depot 3 times weekly After one year no residual tumor One year later symptom f ee
	low	18	28	pelvi tissues	1 000 mg Depot Pro era weekly Imp o ed After 2 years a first size pel ic tumor w thout symptoms.
	med um	49	0	vagina	Proluton Depot 3 times weekly After 4 months no residual tumor One year later symptom free

...ther factors necessary for a satisfactory hormone ...t Teulings (21) however reported 9 cases (with ... of 0–534 and PR of 0–2440 fmol/mg cytosol ...ein) including 4 that responded to treatment with ...esterone 3 of these 4 had progesterone re...ors The fourth like the other 5 had no proges...ne receptors Of 12 cases of recurrent endo...rial carcinoma Ehrlich *et al* (3) found a high PR ...ent in 3 all of which responded objectively to ...esterone therapy compared with only 1 of the ...9 with a low PR content They felt that an ar...ry value of 50 fmol bound H^3 progesterone per ...cytosolprotein could be regarded as indicating a ... PR content in the tumor

...the management of breast cancer determination of both estrogen and progesterone receptors seems to ...ase the reliability of predicting whether any ...onse to endocrine therapy can be expected in a ... case (11 16) Mammary and endometrial ...ers seem to have a similar endocrine background ... any cases and therefore we include both E_2R and ... in our determinations Our results show this to ...ably important from a predictive point of view ... perhaps being the most decisive factor as in 2 of ...E R positive and responding cases no PR was ...onstrable This might however also be explain...y the nature of the specimen if stroma was abun... and epithelial cells sparse One case which was ... – PR positive did not react to gestagens If there ... been any DHT receptors in this case it would ... been interesting to try administration of an...gens Determinations of several receptors might ...ease their clinical value

If carcinoma of the breast does not contain estrogen receptors it will practically never respond to endocrine therapy But if such a tumor does contain receptors it will often respond favorably The estrogen receptor level at which a response to treatment can be expected has been empirically found around 10 fmol/mg cytosolprotein Instead of obviously meaningless endocrine therapy E_2R negative cases one can start agressive cytostatic treatment without unnecessary delay Borderline cases could receive combined hormone and cytostatic treatment Cytostatics seem to be more effective when the tumor has no estrogen receptors (5 13) which could imply a higher degree of malignancy in these cases The absence of estrogen receptors in primary carcinomas of the breast is also believed to be a prognostically unfavorable factor and predicts early recurrence and early remote metastasis irrespective of such well known prognostic factors as the size of the tumor and the presence or absence of axillary metastases (4 11) It appears that no attempts have been made to find out whether any association exists between the presence of receptors on one hand and the occurrence of metastasis to different locations such as the skin vagina lymph nodes liver lungs brain etc on the other Owing to clonal differentiation the metastases might differ from one another and from the primary tumor with regard to the receptors Metastases developing after treatment of the primary tumor might have different receptors from metastases arising before such treatment

Progesterone appearing as an estrogen antagonist reduces the estrogen receptor content of both normal

and malignant endometrial cells (7) so that the cells are deprived of the stimulating effect of available es trogen Synthesis of progesterone receptor protein however requires estrogen If estrogen were given to a patient with endometrial carcinoma in a constantly low dose and progesterone were given intermittently in a high dose it might be possible to destroy neo plastic cells in non responding cases which initally lacked receptors (see also Jänne *et al*)

Adjuvant gestagen therapy might also be useful in the management of endometrial carcinoma in stage I Administration of gestagen in such cases for a period of 2 years in a dose of 500 – 1 000 mg medroxypro gesterone per week plus conventional surgery and radiation appears to give an improved and almost 100 per cent five year survival rate (2) Since such a hor monal adjuvant has virtually no serious side effects objections of the type raised against adjuvant cyto static therapy in mammary or ovarian cancer for ex ample seem not to be applicable to progesterone But even in such cases determination of the estrogen pro gesterone receptors in the primary tumor tissue might be desirable in order to refine and adjust the treat ment and the dose

Measurement of the PR concentration in human endometrial tissues seems to be most accurately accomplished with R 5020 (1) This was the technique we used It has to be stressed however that the tumor specimens were stored deep frozen for up to 3 years *It has been the experience of many authors* and our own that the level of progesterone receptors in mammary carcinoma tissue may decrease strongly under such storage This disturbing fact has to be taken into consideration when the levels of the pro gesterone receptor actually measured are regarded from the quantitative point of view Therefore cur rently in our laboratory tumor specimen are deter mined without delay

No definite correlation was found between E_2R and the patient s age or the degree of differentiation of the tumors in our small study This is of clinical importance if verified on a bigger number of patients

Our findings show that in vitro method of deter mining E_2R and PR can predict the in vivo response of patients with wide spread endometrial tumors to *treatment with progesterone and that this is clinically* useful Cytostatic treatment can be given without delay to E_2R PR negative patients with tumors Fur ther research is needed to investigate whether the syn thesis of absent E_2R PR receptors can be induced in tumor cells It would be interesting to know whether any positive correlation exists between treatment estrogen in cases without E_2R PR content o hand and those with *an increase in* E R PR co on the other This possibility is receiving atte our laboratory and experiments to clear up this p are in progress

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Date	Place	Name	Office
1980			
July 20–23	Williamsburg USA	AAGL Laparoscopic sterilization A comparison of the methods	American Association of Gynecolog Laparoscopists 11239 South Lake B Downey California 90241 USA
September 2–3	Barcelona Spain	Congreso Europeo Perinatal	VII Congreso Europeo de Medicina Perinatal Apartado de Correos No 29015 Barcelona Spain
September 2–5	Barcelona Spain	7th European Congress of Perinatal Medicine	Congress secretariat Apt de Correos 29015 Barcelona Spain
September 2–6	Berlin Germany	6th International Congress of Psychosomatic Obstetrics and Gynecology	Ass Prof Dr M Stauber Frauen Charlottenburg der FUB Pulsstr 4 D 1000 Berlin 19 W Germany
September 4–7	Kiwah Island Charleston SC	International Symposium on Carcinoma of the Cervix Biology Etiology & Diagnosis	E S E Hafez M D OB/GYN State University Medical Res B 4 550 E Canfield Detroit MI 4820
September 15–16	Bologna Italy	First International Symposium on Recent Advances in Prenatal Diagnosis	A C Assistanza Congressi Via P Palagi 21–40138 Bologna Ita
September 22–28	Varna Bulgaria	3rd International Colloquium on Physical and Chemical Information Transfer in Regulation of Reproduction and Aging	Bulgarian Academy of Sciences J G Vassileva Popova c/o Dept of Biophysics 113 Sofia Bulgaria
September 24–26	Kiel West Germany	International Symposium on Fertilization and Artificial Insemination	Priv Doz Dr L Mettler Frauenklinik der Universitet Kiel Hegewischstrasse 4 D 2300 Kiel I
Sept Oct 29–1	Freiburg Germany	International Congress on Endocrinology of Human Infertility	C Ferrari M D P O Box 99 Milan Italy
September 30	London England	Anti androgen therapy for hirsutism	Symposium Secretary Inst of Obs Gynaecol Queen Charlotte's Mat Hospital Goldhawk Road London W6 OXG England
October 3–5	New Delhi India	3rd International Seminar on Maternal and Perinatal Mortality Pregnancy Termination and Sterilization	Hon General Secretary The Fed Obstetric & Gynecological Societies India Purandare Griha 31/c Dr N A Purandare Marg Bombay 400 007 India
November 14–17	Madrid Spain	7 Congrès Europeen de Medecine Perinatale	Professor de la Fuente Maternidad de la Ciudad Av Generalissimo 177 Madrid 16
November 18–23	New Orleans Louisiana USA	AAGL Ninth Annual Meeting Clinical Symposium on gynecologic endoscopy	American Association of Gynecol Laparoscopists 11239 South Lak Boulevard Downey California 90
November 20–22	Barcelona Spain	Symposiuim International Sobre Monitarizacion Prenatal	Instito Dexeus Srtas M Luis Ar Ana Baldrich c/Paseo de la Bon 67 Barcelona 17 Spain

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INTRAEPITHELIAL NEOPLASIA AND CARCINOMA IN THE VAGINAL VAULT

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:t An 11 year biopsy material from the vagina is ed The indication for taking the 370 vaginal biopsies normal cytology polyps or suspicion of tumor The material was found to include 10 cases of in ielial neoplasia viz 4 primary 6 secondary and 2 ies of secondary invasive carcinoma The interval be the primary and secondary diagnosis ranged from 7 to 19 years It is concluded that the risk of secon langes in the vaginal mucosa is slight but cytological up is recommended

ry invasive carcinoma of the vagina was first bed by Cruveilhier (3) in 1827 in an autopsy ial

st authors (1 21) have reported that its share in nancies of the female genitalia amounts to 1 per o 3 6 per cent Carcinoma *in situ* (CIS) of the primary or secondary to neoplastic changes in rvix is stated to be even more rare (5)

'aginal carcinoma is diagnosed at the intraepi l stage the survival time is the same as for CIS cervix (18) Although intraepithelial changes in agina develop but slowly into invasive carci progression to malignancy is on record (9 13))

ce this development has taken place the prog in terms of 5 year survival is considerably :r

1952 Graham & Meigs (6) reported recurrence in agina in patients with a history of hysterectomy itraepithelial neoplasia of the cervix This altered irgical technique so that hysterectomy for cer CIS was made to include removal of the vaginal with thorough histological examination of the cal margins and a more frequent cytological con of the remaining vaginal vault

ie object of the present paper is to survey the ioses and treatment of invasive and intraepi il neoplasia of the vaginal vault from an 11 year id in the Gynecological Department and Path y Department of Frederiksberg Hospital Copen n

MATERIAL

A retrospective review of 370 biopsies from the vagina taken in the Gynecological Department during the period 1 1 1966 to 1 1 1977 on the indication abnormal cytology polyps or suspicion of tumor tissue disclosed 10 cases of intraepi thelial neoplasia in the vagina primary or secondary and 2 cases of squamous-cell carcinoma The biopsies and the cor responding clinical material will be presented below

RESULTS

Table I lists the patients ages the histological or cytological diagnosis on which primary and secon dary treatment was based mode of treatment and length of follow up period

Four of the 12 cases were primary and 8 secondary having previously had intraepithelial neoplasia or car cinoma of the cervix Of the 4 primary cases two pa tients had a history of hysterectomy for benign dis ease (Cases 11 and 12) Positive cytology in subse quent cancer screening indicated biopsy which dis closed vaginal dysplasia and CIS respectively Re peated findings of suspicious cells (Cases 9 and 10) in dicates cervical curettage and biopsies from the portio and vaginal vault In one of these patients (Case 9) conization was done because of dysplasia in the cer vical biopsies Histological examination of the conus showed no abnormalities but there was severe dys plasia in the vaginal vault The other patient (Case 10) exhibited no abnormalities in the cervical smears or biopsies from the portio but mild dysplasia in the vaginal vault Of the 8 secondary cases five (Cases 2 3 4 5 and 8) had previously had cervical CIS one (Case 1) dysplasia and two (Cases 6 and 7) Stage I squamous-cell carcinoma

The primary treatment had been hysterectomy in 7 patients (Cases 1 2 3 4 5 6 and 8) and radium in one (Case 7) The interval between primary treatment and the finding of secondary histological changes of the vaginal vault requiring treatment ranged from 7 month to 19 years

Table I *Age diagnosis and treatment (prim and sec) and period of observation after sec treatment*

Pat no	Age and diagnosis at prim treatment	Prim treatment	Age and diagnosis at sec treatment	Sec treatment	period
1	56 dysplasia	hysterectomy	57 dysplasi	radium	6 y
2	49 ca in situ	hysterectomy	54 dysplasi	0	3
3	35 ca in situ	hysterectomy	36 dysplasi	0	3
4	59 ca in situ	hysterectomy	60 abn cytology	radium	9
5	38 ca in situ	hysterectomy	53 c plano-cellulare	radium + ext radiation	11 yr
6	46 stage Ia	hysterectomy	49 ca in situ	radium + ext radiation	9 yr
7	45 stage Ia	radium	64 ca in situ	hysterectomy + ext radiation	1 yr
8	42 ca in situ	hysterectomy	54 c planocellulare	radium + ext radiation	10 [illegible]
9	54 abn cytology	conization	dysplasia	0	4
10	45 ca in situ	0	dysplasia	0	2 [illegible]
11	47 benign disease	hysterectomy	dysplasia	0	4 yr
12	56 benign disease	hysterectomy	ca in situ	radium	9 yr

repeated

Secondary treatment Three (Cases 9 10 and 11) of *the four patients with primary intraepithelial changes* in the form of dysplasia received no treatment as repeated cytological studies showed no abnormalities *One patient (Case 12) with CIS was treated with radi*um The follow up period is from 2–9 years and no patient has shown signs of recurrence

Out of the 8 secondary cases two patients (Cases 2 and 3) with dysplasia in the vaginal vault received no treatment as the cytological findings were negative during the next 3 years One patient with dysplasia (Case 1) and persisting positive cytology was treated with radium Four patients (Cases 4 5 6 and 8) one of whom had repeated abnormal cytological findings two squamous cell carcinoma and one CIS of the vaginal vault were treated secondarily with radium the last 3 (Cases 5 6 and 8) also with external roentgen radiation Six of these 8 patients had been free of recurrence during a follow up period of 3–11 years while one (Case 8) developed in the course of a few months a vesicovaginal fistula and recurrence of the tumour in the entire vaginal wall and on the labia majora Finally Case 7 who had been treated 19 *years previously with radium for cervical carcinoma* underwent hysterectomy The operation was not radical and one year later it was supplemented with *external roentgen radiation because of tumour* tissue in the vaginal vault

DISCUSSION

Theories concerning the pathophysiology of neoplasia in the vagina have been advanced by Palmer & Spratt (16) among others They believed *condition could be induced by irradiation* vagina in low doses which had a stimulating upon the growth of abnormal cells in the vagi*ly one of the present patients had primarily* treated by radium Newmann & Cromer (1 others (2 4 11 14) later suggested the theor *multicentric origin of carcinoma in the vagina* and vulva They believed that the tumor iss from multiple mutually independent foci pe a result of a common carcinogenic *stimulus* workers (8 9 18) have demonstrated carcin carcinoma *in situ* in the vulva as well as cer vagina of the same patient Only one of the p in the present material had changes in the vulva 8)

Table I shows a difference of up to 19 years 7 years) in the patients ages at primary dary diagnosis It is a natural explanation that velopment of intraepithelial changes is ver slow and possibly starts later in the vagina tha cervix However changes of the vaginal mucos have been present at the primary treatment be escaped diagnosis Similar intervals in age ha reported by others (5 9 10)

The primary as well as the secondary treatme *carried out in the* Gynecological Department primary cases were diagnosed in the cours cancer screening programme in the municip Frederiksberg and the 8 patients with sec changes had been followed in the Out patient for 5 years after primary diagnosis and trea

most common abnormal but guiding finding positive cytology No patient had vaginal dis ge spotting or post coital bleeding If the portio been preserved a positive smear may lead to the nosis and treatment of a possible cervical disease ling the risk that dysplasia or CIS of the vaginal t is overlooked

posthysterectomy patients positive cytology ld always be followed by staining of the vaginal t with Schiller s solution followed by biopsy Ac ing to Schiller (19) the test is based upon the fact normal squamous epithelium is high in glycogen stains brown with a solution of iodine whereas pithelium with intraepithelial changes or carci a is devoid of glycogen and therefore remains un ed Experience has shown however that certain gn diseases (hyperkeratosis erosion metaplasia) remain unstained and that conversely mild to erate dysplasia and even carcinoma *in situ* or in e carcinoma may stain with a solution contain odine However although the Schiller test may d a false positive result in benign diseases and a negative result in malignancy (17) it is still being because of its simplicity by many gyne gists to demarcate mucosal areas to be biopsied nized Colposcopy of the vaginal vault may pos be used

rophic mucosae in postmenopausal women ld be treated with estrogen prior to the Schiller and biopsy since atrophic epithelium usually not contain the quantities of glycogen needed dine staining Invasive vaginal cancer following hysterectomy for carcinoma *in situ* is rare The nt material includes two cases of squamous-cell noma in the vagina diagnosed 15 and 12 years primary treatment

interval of many years between the demonstra of mucosal changes on the portio and in the ia (5 9 18) supports the theory of a multicentric n On the other hand a recurrence within the 3 years after primary treatment in 4 patients may xplained by the operation not having been al leaving precancerous changes in the vaginal Thus revision of the microscopic preparations led dysplasia in the surgical margins in 3 of the nts but no abnormality in the fourth

cases indicating removal of the uterus because of epithelial neoplasia in the cervix most authors 12) agree that the uppermost centimetre of the na should be removed as well Empirically the rare recurrences are nearly always situated in the vaginal vault and indeed this was so in 7 out of the 8 patients in the present material despite removal of the vaginal vault at the time of hysterectomy Only one patient (Case 8) had malignant changes in the en tire vagina as well as in the vulva

When treating intraepithelial neoplasia of the vaginal vault a few workers (7 9) prefer local excision instead of radium in order to avoid its side effects Five of the present patients received no secondary treatment because of subsequently negative cytology The changes observed had presumably been removed by the biopsy forceps

CONCLUSION

Early diagnosis of a recurrence of intraepithelial neo-plasia in the vagina is important As there is a pos sibility of subsequent invasive carcinoma cytological study should probably not be omitted in patients with a history of hysterectomy for benign disease although in such cases there is little risk of in traepithelial and invasive carcinoma of the vagina Total hysterectomy for CIS or dysplasia should in clude the uppermost centimetre of the vagina In spite of a minimal risk of recurrence continued follow up of these patients by smear tests is advisable especially as they often do not have symptoms It is recom mended to continue the follow up for many years perhaps for life In the event of positive cytology the vagina should be stained with iodine possibly after preceding estrogen therapy and biopsies taken from non staining areas Colposcopy may afford guidance

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EFFECT OF ESTROGEN/PROGESTOGEN COMBINATIONS ON POLYMORPHONUCLEAR LEUCOCYTE CHEMOTAXIS

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act The effects on leucocyte chemotaxis and on the d lymphocyte culture reaction were studied in fourteen n taking estrogen/progestogen combinations An in in leucocyte chemotaxis was found during hormonal nent and sera from these women were found to inhibit ixed lymphocyte culture reaction

bined estrogen/progestogen preparations are us y numerous healthy women over prolonged ds for hormonal contraception or substitution id the menopause Recent data suggest that ig the variety of clinical effects following such nic therapy some may reflect interference with ine mechanisms (12 21) Estrogen seems to have hibitory effect on the thymus (15 19) and in atory animals the administration of estro- rogestogen has prolonged the survival of homo (14 15) During human pregnancy a depressed vity of the maternal T lymphocytes has been nstrated in several investigations (18 23) It has een shown that plasma or serum from pregnant n has immunosuppressive properties (5 13 24) ilar reactions have been observed in women g oral contraceptives (1 2 9) but the results are icting (6) Women taking oral contraceptives been reported to have an increased risk of oping chicken pox (varicella) and a decreased of non toxic goitre thyreotoxicosis myxedema heumatoid arthritis

lymorphnuclear leucocyte (PMN) function is an rtant part of the immune response and an in ed phagocytic and bactericidal activity during ancy has been reported (16) So far we have d no reports concerning neutrophil leucocyte ion during estrogen/progestogen treatment In resent investigation neutrophil chemotaxis was ured in women during such treatment and the ef of serum on control leucocytes and the mixed hocyte reaction were studied

MATERIAL AND METHODS

Subjects Fourteen women were studied before and after 2 months of treatment with estrogen/progestogen prepara tions Eight women age range 41 – 56 years were treated with a combination of estradiol valerate 2 mg/norgestrel 0 5 mg (Cyklabil[R]) and six women range *16 – 23 years* were treated with etinylestradiol 0 03 mg/norgestrel 0 15 mg (Follimin[R] Neovletta[R]) All women were apparently healthy taking no other drugs and there were no clinical signs of infections or other diseases during the observation period

Chemotactic assay Leucocyte chemotaxis was studied in modified Boyden chambers by the leading front technique of Wilkinson (25) Ten ml of venous blood samples were al lowed to sediment in plastic tubes for 30 minutes at 37 C in the presence of 2 ml 1 per cent metosel solution The leuco- cyte rich supernatant was diluted in Gey s solution pH 7 2 (25) and centrifuged at 500 × g for 5 minutes The cells were washed 3 times and finally resuspended in Gey s solution to a final concentration of 1×10^6 cells per ml The cell sus pension (0 2 ml) was placed in the upper part of the chemo- taxic chamber In the lower part was placed *a)* 3 6 ml of Gey s solution as negative control or *b)* 3 6 ml of casein so- lution (5 mg casein per ml Gey s solution) (6) The chambers were incubated at 37 C for 20 minutes and the filters (porosity 3 microns/Sartorius Inc Göttingen Germany) were then removed fixated and stained (6)

The filters were inspected at the magnification of × 400 and the distance travelled by the leading front leucocytes was measured as the mean of 5 different fields Each experi ment was duplicated In this system chemotaxis of controls ranges 100 to 130 microns The mean values±SD of chemo- taxis for seven healthy control donors before and after the investigation period were 121 5±21 7 and 114 9±12 7 microns respectively

Incubation of control leucocytes To evaluate separately cel lular and humoral factors serum samples from the treated women were used for incubation of leucocytes from healthy untreated donors prepared as described above Incubation with patients sera was allowed for 1 2 and 24 hours at 37 C Chemotaxis of control cells was then performed as described

Mixed lymphocyte culture Venous blood from unrelated healthy nonpregnant donors was defibrinated by gentle agitation with glass beads The lymphocytes were separated by centrifugation on a layer of Ficoll Isopaque (4) The cells were washed 3 times and suspended in medium RPMI 1640 containing 20 mmol/l Hepes (Flow Laboratories) Strepto-

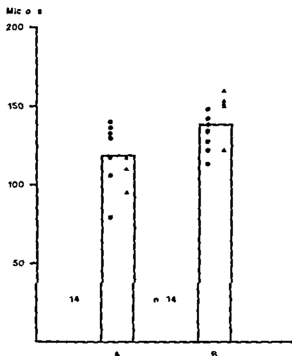


Fig 1 Neutrophil chemotaxis before (A) and after (B) hormonal treatment Filled circles represent women taking estrogen/progestogen for climacteric disorders filled triangles women taking oral contraceptives

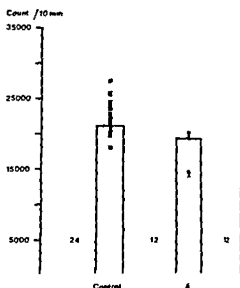


Fig 2 Comparison of the mixed lymphocyte tween control cultures containing autologous tures containing patient s serum (A) and after hormonal treatment (B) Filled ent women taking estrogen/progestogen for orders filled triangles women taking oral contrac

mycinsulphate was added in 100 ug per ml of medium Wells of Falcon Microtest II tissue culture plates (Gateway International Los Angeles) were filled with 150 μl of mixed lymphocyte suspension with equal numbers of lymphocytes from each of two donors To each well 50 μl of serum from one of the investigated women or autologous serum was added The final concentration of lymphocytes was $1\ 5 \times 10^6$ per ml All tests were done in triplicate The microplates were closed with a plastic film and incubated at 37 C for 6 days Five hours before the end of the incubation period 0 04 μCi of [^{14}C] thymidine in 20 μl saline was added to each culture Cultures were washed and precipitated on glass fibre filters by a semiautomatic multiple sample processor and the radioactivity was determined in a scintillation counter Quenching estimated by the external standard method was very similar throughout each experiment and therefore results were expressed as the average of the counts per minute obtained in triplicate tests

RESULTS

Neutrophil chemotaxis before and after hormonal treatment is shown in Fig 1 The migration increased from 118 2±7 4 microns (mean±SD) to 137 9±13 7 microns Using Student s t test for paired observations the increase was highly statistically significant for the whole group ($p<0\ 001$) and for the subgroup of six women taking 0 03 mg etinylestradiol ... norgestrel ($p<0\ 001$) The random m... 23 3±3 4 microns (mean±SD) before and ... microns after 2 months of treatment ... control donor leukocytes with patient ... after 2 months of treatment gave no ... changes in migration for any of the three ... periods used

The influence of patients sera on the mixed ... phocyte reaction using lymphocytes prepared ... unrelated control donors is shown in Fig ... was no difference between control cultures c... ing autologous serum and cultures contain... sera before hormonal treatment A significant ... sion of lymphocyte reactivity was found in c... incubated with sera from women after 2 m... hormonal treatment This was true for the ... group ($p<0\ 01$) and for the subgroup of ... taking estradiol valerate 2 mg/norgestrel ... (Cyklabil[R]) ($p<0\ 05$)

DISCUSSION

Chemotaxis adherence phagocytosis and ... lar killing of microbes are fundamental func... polymorphnuclear neutrophil leucocytes ...

ical conditions with various defects in this system an increased susceptability to infectious diseases e been described (20) A decrease in neutrophil motaxis is known to occur during treatment with ie antibiotics (21) So far we have found no data erning this aspect of host defence during com d estrogen/progestogen treatment in women and hermore few factors are known to increase notaxis Ascorbic acid (8) and certain infections have been reported to increase chemotaxis as well he spontaneous random migration Recently ll doses of alcohol were found to increase neu hil chemotaxis in an in vitro experiment (10)

uring pregnancy the neutrophil phagocytic func has been reported to increase (16) The increased notaxis found in this study seems to be due to *lar factors* since incubation with serum did not e any change in the migration capacity of control ocytes Neutrophil chemotaxis is influenced by phocytes since lymphokines have been shown to depress and to increase chemotaxis (22) Dur pregnancy there is a depressed T lymphocyte tion and a few reports have described a similar omenon in women taking oral contraceptives (1

In the present study sera from women during ional treatment gave an inhibition of the MLC ion from unrelated control lymphocytes It is established that pregnancy plasma has the same erties It might be that depression of lympho during hormonal treatment may reduce lym ine activity resulting in an increased neutrophil ity An increase of neutrophil chemotaxis and an ition of T lymphocyte activity might represent of an altered immune response during combi strogen/progestogen treatment Further studies iecessary to clarify whether these observations any relation to the increased susceptability to in viral infections and autoimmune diseases re d in women undergoing such therapy

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ULTRASTRUCTURE OF CELL DETACHMENT FROM THE HUMAN FETUS IN EARLY PREGNANCY

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ract The recently confirmed value of amniotic fluid cy gy as a tool in the determination of fetal maturity con tes the background of the present study in which the hative capacity of human fetal skin was investigated correlate ultrastructural methods By transmission and ning electron microscopy detachment mechanisms are dated in the fetal periderm It is concluded that the ex tive capacity prevailing in early pregnancy fetal skin is rent from the maturity related exfoliative capacity in hird trimester Both kinds of exfoliated cell material stute antenatally available fetal tissue the utilisation of h in antenatal diagnosis may be extended

origin of cells in the amniotic fluid has recently investigated in the Rhesus monkey and in the an in early and late pregnancy (11 2 3) These rts are concerned mainly with the cell pattern in amniotic fluid as an expression of the tissue diffe ation in the fetus Using cytology tissue matura can be determined with high accuracy in par ar in risk cases complicated by meconium con nation of the amniotic fluid where biochemical sment of phospholipids is unreliable (7 8)

early pregnancy cell morphology of the amniot uid has been studied only to a small extent due to limited information obtainable from these cells pt by chromosome analysis In the light of recent ings in late pregnancy concerning maturity deter ation by cytology however a growing interest is eable regarding the contribution in early preg y of various tissue surfaces to the cell contents of iotic fluid A striking difference in the degree of chment of cells to the fluid has been shown ntly the amniotic epithelium virtually lacking ex itive capacity while fetal periderm displays heavy liation (2) The nature of this phenomenon is ear as is its occurrence in some ectoderm vates but not in others

The cells and cell fragments detached to the am niotic fluid may constitute messengers emitted from the fetus in early pregnancy These tissue fragments are unique because of the ease by which they are obtained as the first tissue samples available from the fetus *in utero* In a future widening of the field of antenatal diagnosis the understanding of the site of exfoliation and the nature of cell detachment from certain epithelia will probably elucidate the role of these cells and what they express The purpose of the present study was to correlate parallell transmis-sion (TEM) and scanning electron microscope (SEM) findings on the formation of cells and cell fragments from the fetal periderm

MATERIAL AND METHODS

Tissue material was harvested from 10 pregnant women in 16th to 19th week undergoing hysterotomy for legal abor tion The amniotic sac was evacuated and torn in 2 5 per cent glutaraldehyde in Soerensen s phosphate buffer pH 7 4 After immersion in the fixative for at least a few days the material was dissected and specimens of skin from the thigh and the back were exised in small portions for further preparation After rinsing specimens in Soerensen s buffer they were postosmified in 1 per cent osmium tetroxide in the same buffer

For TEM specimens were processed in a dehydration series to absolute ethanol and then gradually to propylene oxide and Epon Sections for light microscopy were taken and toluidine blue stained and representative areas selected for fine sectioning on an LKB ultrotome The fine sections were stained with uranyl acetate and lead citrate A Philips 300 A transmission electron microscope was utilized

For SEM specimens were taken through three baths of redistilled water frozen with a minimum amount of water by plunging the tissue pieces in a quenching medium of iso-penthane chilled by surrounding liquid nitrogen Freeze drying was carried out at about −17 C (dry ice) for 2−3 days After mounting on SEM stubs sputter coating with gold was carried out A JEOL JSM U3 scanning electron microscope was used run at 15− 0 kV

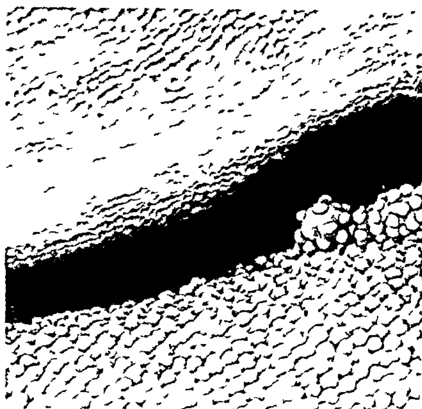


Fig 1 Survey over fetal
week Note bulging cells
instances partially
the peridermal surface
electron microscopy

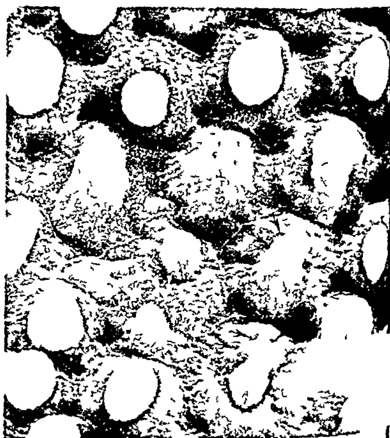


Fig 2 Cell fragments in various stages of *exfoliation* from human periderm 19th week Delicate strands of intercellular borders constitute a polygonal pattern of fetal skin cells In the center of each cell a protrusion is formed densely microvillous and gradually undermined by several indentations (arrows) Scanning electron microscopy magn 1 700 ×



Fig 3 Detachment of cell fragments from polygonal cells of fetal skin (periderm) Note visible stalks (arrows) carrying two structures apparently liberated from the periderm to the amniotic fluid The microvillous surface and the different stages of exfoliation are visible Scanning electron microscopy magn 2 500 ×



4 Transverse section through fetal periderm week showing skin surface uppermost with cell fragments in the course of exfoliation two indentations (arrows) near the base of protruding cell fragment forming microvilli d cavities (cf Fig 6) The most superficial cell r is the fetal periderm (P) while underneath germinative layer is distinctly multilayered also abundance of glycogen granules (G) nsmission electron microscopy magn 2 500 ×



Fig 5 Glycogen lad[illegible] fragment under exfo[illegible] from fetal periderm [illegible] amniotic fluid No [illegible] lous surface and [illegible] granules (G) The germ[illegible] layer (GL) and perider[illegible] are attached to each ot[illegible] a system of desmosome[illegible] Fig 7) Transmission e[illegible] microscopy magn [illegible]

RESULTS

Surface ultrastructure of the skin specimens investigated showed features of extensive detachment of cells and cell fragments Both in TEM and in SEM there was a striking uniformity of the exfoliation procedure Several distinct stages of detachment could be detected and confirmed by means of both techniques The earliest sign of a forthcoming exfoliation was the occurrence of a dense microvillous lining on a convex cell surface This lining was typically more dense towards the center of the microvillous area (Figs 1–2) Gradually the center was slightly elevated to form a rounded densely microvillous prominence In this slight elevation small pits and minor invaginations were obvious in the lowermost portion (Figs 3–4) By and large these pits coalesced to form confluent spaces below the continuously more bulging prominence (Fig 5) In the periphery of the protrusion an invagination took place and brought about further undermining of the protrusion The confluence spaces below the protrusion showed a microvillous lining surrounding a secretion mostly amorphous but sometimes granular (Fig 6)

Exfoliation to the amniotic fluid always occurred from the outer layer (periderm) while the second layer (germinative layer) never showed any signs of cell surface detachment Between these layers an extensive network of desmosomes was conspicuous (Fig 7) All along the thin unicellular periderm th[illegible] desmosomal connections to the germinative [illegible] underneath In both layers a prominent featu[illegible] the occurrence of an abundance of glycog[illegible] either as single particles or as rosettes (Fig 8) [illegible] was a gradual loss of glycogen granules [illegible] deeper parts of the germinative layer

Tonofilaments were predominant in the perider[illegible] cytoplasm (Figs 9–10) and were particularly c[illegible] trated around the cell membrane indentations [illegible] coalescing pits The filaments were closely inter[illegible] ed with areas of glycogen granules The und[illegible] of elevated globular cell portions brought a[illegible] tonofilament rich areas of the peridermal cy[illegible] seemed to progress to a continuous decrease in th[illegible] toplasmic communication between exfoliat[illegible] fragment (or cell) and the peridermal mo[illegible] The end result as illustrated by SEM could b[illegible] firmed by TEM as protruding pedicles of cyto[illegible] seemingly remnants of cytoplasmic bridges fr[illegible] periderm to the cytoplasmic portion recently p[illegible] off in the exfoliation process

DISCUSSION

The outer surface of peridermal cells is end[illegible] a capacity to create membrane protrusions [illegible] crease the available periderm area Dur[illegible]



Transversely cut indentation undermining exfoliating …gment to the amniotic fluid The microvilli present …e same appearance as on the surface of the detaching …gments Note finely granular ultrastructure of the …on present in the indentation Transmission electron …copy magn 90 000 ×



Fig 7 Attachement zone between periderm (P) and germinative layer (GL) of human fetal skin 19th week Note distinct desmosomes (D) connecting the two layers and also an apparent direct communication between the two cytoplasms (arrow) Transmission electron microscopy magn 90 000 ×

…ation of the epidermis *in utero* this capacity is …ssed only during a rather limited period of gesta… ranging from around the fourth to the sixth …n of pregnancy (5) Prior to the sixth month the …epiderm is built up with a multilayered ger…ive part and a superficial monolayer the …erm From the seventh month onwards a …m corneum is established and the periderm is …ct to regression (4) During the active period …oned the fetal periderm is strikingly different … the other important component of the lining of …mniotic cavity the amniotic epithelium which …ngly lacks the capacity of membrane motility …cteristic of fetal periderm (2 1)

…e exfoliative behaviour of fetal periderm runs …omitantly with various membrane events leading … vast plasma membrane area exposed to the am…c fluid These events suggest that fetal periderm … only a protective layer shielding the fetus but also an active participant in transport phenomena between fetus and amniotic fluid The occurrence of cytoplasmic vesicles subjacent to the outer peridermal plasma membrane would support the suggestion of exchange across peridermal cells (4)

Membrane motility in the cell area facing the amniotic fluid but not in the area facing the germinative layer could be explained by the conspicuous network of desmosomes connecting the peridermal monolayer to the germinative cells underneath The occurrence of an abundance of tonofilaments in peridermal cells particularly around indentations and coalescing pits suggests that these filaments are somehow related to membrane motility This suggestion seems validated by the close interrelationship between filaments and glycogen granules as evidenced in the present study Energy built up in animal cells in the form of carbohydrates is usally stored as glycogen Most cells in the periderm and the germinative layers were virtually

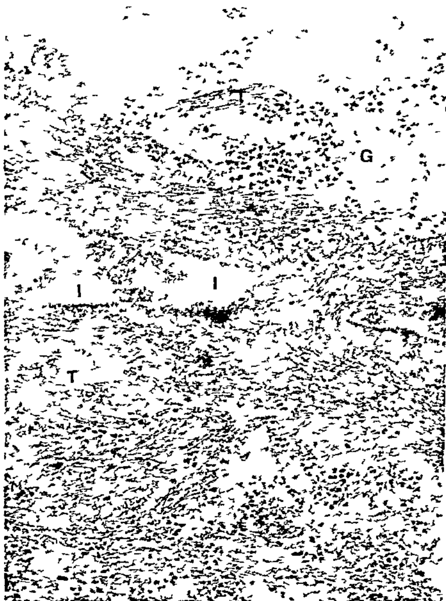


Fig 8 Glycogen gran are *often* interming tonofilaments (T) a uppermost part of the ture In the lower a more scattered ment of single glycog ticles and dispersed ments is evident A lous indentation (I) is the middle Trans electron microscop 60 000 ×

stuffed with glycogen granules The origin of these granules is not known but an exchange between peri *dermal glycogen and amniotic fluid glucose* has been suggested (10) Presumably the exfoliation of glycogen laden cells and cell fragments from the periderm mal surface will account for a net contribution of glucose to the fluid since these detached cell portions are rapidly disintegrated in the amniotic fluid (6)

In various mammals the exfoliative capacity of fetal skin in late pregnancy is described (9 11) It seems as if the extensive exfoliation in the human periderm in early pregnancy is a phenomenon that differs from the detachment of squames from the fetal epidermis during the last months of pregnancy The late cess is used as a tool in maturity determina *thus reflects the differentiation of fetal* epider an index of fetal maturation it appears to run p to the crucial lung maturation and is moreove alent to available phospholipid determinatio ods in predicting fetal maturity In this phase man pregnancy the layer responsible for ex to the amniotic fluid is no longer the perider rather the germinative portion of the orig layered epidermis

To conclude there seem to be two dis foliative mechanisms operating in the fetal



The close interrelationship between bundles of aments and groups of glycogen granules suggests a nal relation to exfoliation capacity of periderm ıssion electron microscopy magn 90 000 ×

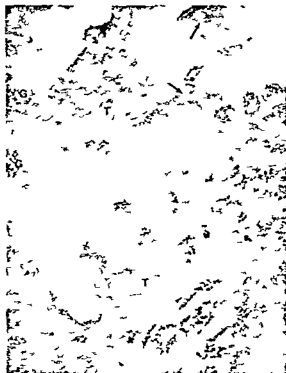


Fig 10 Close up of early indentation of human periderm starting an apparent closure of bridging or branching microvilli (arrows) Note uniform shape of microvilli close to which are observed tonofilaments (T) and scattered glycogen granules (G) Transmission electron microscopy magn 90 000 ×

; human pregnancy They are not active simul usly but during two fairly well defined time peri early and late pregnancy respectively In early ancy a detachment of glycogen stuffed cytoic portions prevails while in late pregnancy a ıment of keratinized cells is predominant The r kind of material can be used for various pur in early pregnancy while the latter kind can be for determination of fetal maturity Both kinds itute antenatally available tissue material from etus whereby the fetal condition may be eluci

ACKNOWLEDGEMENTS

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ULTRASONIC MEASUREMENT OF FETAL BODY SIZE

A randomized controlled trial

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ract A total of 745 Caucacian women were allocated at om between two groups A and B at the first antenatal At the completion of the study 341 patients in group derwent a single ultrasonic measurement of fetal chest between 32 and 36 weeks of gestation The medical was not informed of these results Three hundred and four patients in group B acted as controls

e percentage of clinically detected small for dates D s) was low in both groups A (36 per cent) and B (42 ent) The ultrasonic detection rate of the clinically d S F D s (group A) was 77 per cent

e clinical detection rate of large for dates (L F D s) nly 12 per cent in group A and 13 per cent in group B ltrasonic detection rate of the clinically unrecognized) s (group A) was 60 per cent

the last couple of years a stream of information merged on the value of ultrasonic measurement tal head and body size relative to fetal growth data indicate that fetal chest and upper ab- nal size are more sensitive parameters for the de n of abnormal growth than fetal biparietal di r (B P D) (1 2 3 4 5 8 10 11 12) This presents the results of a randomized controlled n the significance of a single 3rd trimester ultra measurement of fetal chest area in detecting and large for-dates infants

MATERIAL AND METHODS

l of 745 Caucacian women was included in the study were divided into two groups A and B depending on ooking number at the first antenatal visit (even ers to group A odd numbers to group B) Each pa n group A was sent to the Ultrasound Department for le chest area measurement between 32 and 36 weeks of ion The medical staff in the out patient s department ot informed of the results The patients in group B l as controls

oth groups antenatal care included a single B P D rement before 25 weeks gestation in case the onset of st menstrual period was in doubt and assessment of growth by serial abdominal palpation and measure- of the distance between the upper rim of the pubic and uterine fundus using a tape measure When there was a negative or positive discrepancy in fundal height of two weeks or more or any other abnormal antenatal find ing the patient was referred to the Ultrasound Department In these instances the medical staff was informed of the ultrasonic data obtained

Ultrasonic measurement of the chest area was performed caudal to the fetal heart pulsations using a sound velocity of 1 540 meters per second (10) The 5th and the 95th centile of the chest area curve based on 302 normal pregnancies be tween 23 and 42 weeks of gestation were used as the lower and the upper limit of the normal range (11) Birth weight was defined as being between the 10th and 90th centiles (normal) below the 10th centile (small for-dates) or above the 90th centile (large for-dates) according to the Tables of Kloosterman (6) correction being made for maternal parity and fetal sex

RESULTS

At the completion of the study group A consisted of 341 and group B of 364 patients since in both groups patients had dropped out due to mid trimester abor tion premature delivery intra uterine death or omis sion to refer the patient to the Ultrasound Depart ment The mean lag between ultrasonic measurement of fetal chest area and date of delivery was 32 days (range 4 – 71 days) in group A and 36 days (range 2 – 64 days) in group B Further results will now be presented in relation to fetal birthweight

Normal birth weight (n = 603) In group A (n = 295) 257 patients were scanned solely in relation to the project (non referrals) Fetal chest area was situated below the normal range in 9 and above this in 3 cases

Thirty eight patients in group A were referred to the Ultrasound Department due to a negative (n = 26) or positive (n = 12) discrepancy in fundal height Fetal chest area fell below the normal range in 3 and above this in 2 cases

In group B (n = 308) 18 patients were sent for an ultrasonic examination because of a negative discrep- ancy 13 patients because of a positive discrepancy Fetal chest area fell below the normal range in 2 and above this also in 2 cases

Table I *Clinical and ultrasonic detection rates of small for dates in groups A and B*

	Group A (n = 28)				Group B (n = 33)			
	Clinically detected		Clinically undetected		Clinically detected		Clinically undetected	
	5–10%	<5%	5–10%	<5%	5–10%	<5%	5–10%	<5%
Ultrasonically detected	6	3	10	4	4	9	12	7
Ultrasonically undetected	1		4		1			

never referred to Ultrasonic Department

Small for dates (n = 61) Table I presents the clinical and ultrasonic detection rates of small for dates (S F D s) for groups A and B

In group A (n = 28) the number of clinically detected S F D s was 10 (36 per cent) 9 of these 10 S F D s were also diagnosed by ultrasound

In the 18 clinically missed S F D s birthweight varied between the 5th and 10th centile in 14 and below the 5th centile in 4 cases In the 5–10th centile weight range 10 S F D s (71 per cent) were recognized during ultrasonic examination In the weight range below the 5th centile all 4 S F D s were detected by ultrasound

In group B (n = 33) the number of clinically recognised S F D s was 14 (42 per cent) 5 (30 per cent) fell in the 5–10th centile weight range (n = 17) 9 (56 per cent) were situated below the 5th centile (n = 16)

Of these 14 clinically detected S F D s 13 were also diagnosed by ultrasound Nineteen S F D s remained undetected and were therefore never referred for ultrasonic examination

Large for dates (n = 41) Table II gives the clinical and ultrasonic detection rates of large for dates (L F D s) in groups A and B

In group A (n = 18) only 3 L F D s ed clinically 2 of these were recognized b sound In the 15 clinically undetected L F D weight was situated between the 90th and 95t in 9 and above the 95th centile in 6 cases former weight group 5 (55 per cent) in the la per cent) L F D s were detected by ul group B (n = 23) the number of clinically L F D s was only 3 (13 per cent) one situated in the 90–95th centile weight ran clinically diagnosed L F D s were trasound Of the 20 L F D s which missed 11 (55 per cent) fell in the 90th–95t weight range 9 (45 per cent) fell abo tile weight for gestation

DISCUSSION

In the normal birthweight range the the Ultrasound Department for negative discrepancy in fundal weight was low in 13 per cent in group A and 9 5 per cent in g The percentage of false positive ultrasonic res

Table II *Clinical and ultrasonic detection rates of large for dates in groups A and B*

	Group A (n = 18)				Group B (n = 23)			
	Clinically detected		Clinically undetected		Clinically detected		Clinically undetected	
	90–95%	>95%	90–95%	>95%	90–95%	>95%	90–95%	>95%
Ultrasonically detected	1	1	5	4	1	2	11	9
Ultrasonically undetected		1	4	2				

never referred to Ultrasonic Department

l chest area situated outside the normal range) 13 and 10 per cent in the referrals of group A and nd only 4 5 per cent in the non referrals in group The marked difference between the non referred referred patients may be explained by the fact in the latter fetal birthweight was often situated r or on the 10th or 90th centile

he percentage of clinically detected S F D s is ppointingly low in both group A (36 per cent) and 12 per cent) *This is particularly so in the 5–10th* tile weight range Similar observations have been le by others MacLaurin (7) stated that only about per cent of those fetuses which ultimately fell w the 10th centile weight for gestation were sus ted during the antenatal period Campbell (2) nd that only 41 per cent of a group of 115 babies a birthweight below the 5th centile were recog d clinically Tejani (9) stated an even lower per age of 33 per cent The ultrasonic detection rate e clinically undiagnosed S F D s (group A) is 77 cent (5–10th centile weight range 71 per cent w the 5th centile 100 per cent) The ultrasonic ction rate of the clinically established S F D s is high 90 per cent in group A and 93 per cent in p B The clinical detection rate of L F D s was worse than that of S F D s 12 per cent of p A and 13 per cent in group B This is not sur ng since the obstetrician is more aware of a tive than a positive discrepancy the former in cular being associated with a raised perinatal ality and morbidity rate The ultrasonic detec rate of the clinically unrecognized L F D s was er cent (55 per cent in the 90–95th centile weight e and 67 per cent in the weight range above the centile) This detection rate is somewhat lower the 80 per cent diagnosed in an earlier study

n be concluded that the data presented here sup- the need for routine ultrasonic measurement of chest size in the early diagnosis of the under and sized infant This is particularly so for the so- d borderline underweights i e in the 5–10th les weight for gestation

is realized that routine ultrasonic scanning of an e obstetric population has considerable practical equences A single measurement of fetal chest or abdominal size at 32–36 weeks of gestation would however certainly ease the workload com pared with a combined measurement of both fetal body and head size

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Date	Place	Name	Office
Continuation			
December 1–4	Kairo Egypt	Second Congress of the International Society for the Study of Hypertension in Pregnancy	Docent Hjördis Robbe Dept of Obstet and Gynecol Karolinska Hospital S-104 01 Stockholm 60 Sweden
December 1–12	Melbourne Australia	Seventh UICC Training Course in Cancer Research	Dr A W Burgess UICC Course, The Walter and Eliza Hall Ins... Royal Melbourne Hosp P O ... Victoria Australia
1981			
January 26–31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Congr Adm... 31600 West Chicago Livonia, MI ... USA
March 22–26	West Berlin West-Germany	IIIrd World Congress of Human Reproduction	Dozent L Mettler Frauenklinik Hegewischstr 4 D-2300 Kiel 1
June 9–12	Ostend Belgium	Third International Congress on the Menopause	The International Menopause Soc... 8 av Don Bosco 1150 ...
August 24–28	Cambridge England	XIII Acta Endocrinologica Congress	Conference Services Ltd XIII Acta Endocrinologica Congress 3 London SW7 3ES England
Sept-Oct	Athens Greece	VIth European Congress on Sterility (ESCO)	Sekretariat Prof Dr K Semm klinik der Universität Kiel Hegewisch strasse 4 2300 Kiel 1 West Germ...
October 25–31	Melbourne Australia	Eight Asian Congress of Obstetrics and Gynecology	The Organizing Secretary VIIIth Congress of Obstetrics and Gy... G P O Box 2195T Melbourne ... Victoria Australia

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[M]ATERNAL AND FETAL METABOLIC RESPONSES TO RITODRINE IN THE SHEEP

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[Abs]tract Ritodrine hydrochloride was infused intravenous [fo]r 60 minutes into pregnant ewes or for 29 minutes into [feta]l lambs during the last third of gestation The maternal [and] fetal acid base balance and carbohydrate status was de[term]ined prior to during and after the ritodrine infusions [Rito]drine was also infused into pregnant sheep in labor until [f]urther inhibition of uterine activity could be achieved [In th]ese studies acid base balance was frequently assessed [Th]e maternal or fetal infusion of ritodrine resulted in no [majo]r changes in maternal or fetal acid base balance during [the p]eriods of study Lactate and pyruvate concentrations in [mo]ther and fetus rose during the infusion The lac[tate] pyruvate ratio remained stable suggesting an increase [in bo]th aerobic and anaerobic glycolysis Maternal glucose [conce]ntrations were significantly elevated after one hour of [r]itodrine infusions to the ewes but minimally elevated [in th]e fetus Fructose concentrations were unchanged The [possi]ble role as fetal fuels of increased metabolic products [of g]lycolysis caused by beta adrenergic stimulation is [discu]ssed

[Ther]e is evidence which suggest that beta adrenergic [agent]s may be useful in treating fetal distress (5 10 [) p]ossibly by decreasing fetal respiratory acidosis [...]. It has also been reported that fetal growth is im[prove]d (20 3) and that the incidence of respiratory [distre]ss syndrome is decreased (2) with the use of ma[terna]lly administered beta adrenergic agents

[Ho]wever conflicting reports have also been pub[lishe]d concerning the effects of beta adrenergic stim[ulati]on on fetal acid base balance Increased acidosis [has b]een reported in hypoxemic fetuses and this has [been] attributed to increased glycogenolysis and [glycol]ysis (9 21 13)

[In] view of the uncertain effects of beta adrenergic [agen]ts on acid base balance and glucose metabolism [we st]udied the metabolic effects of one of the beta [adren]ergic agents ritodrine hydrochloride (Philips [Roxa]ne Lab Inc Columbus Ohio) in the chroni[cally] prepared pregnant sheep

MATERIAL AND METHODS

[Anim]al Preparation We used 43 sheep with 36 singleton [and 7] twin gestations Operation for insertion of maternal [and f]etal catheters was performed at 100 to 145 days of gestation The general surgical procedure has been described in detail previously (17 18) Briefly polyvinyl catheters were inserted into a maternal and fetal femoral artery and vein and into the amniotic cavity Following closure of the uterus and abdomen the catheters which had been exteriorized to the maternal flank were filled with heparin and sealed with a metal plug Kanamycin 250 mg was injected into the amniotic cavity for 4 days The animals were brought daily in mobile cages into the laboratory where the catheters were only flushed or the experiments performed

Experimental Design Experiments were usually performed three to five days after surgical preparation (range 2 to 27 days) The ewes had free access to alfalfa pellets and water during the studies Prior to any ritodrine infusion the steady state of the animal was assessed for one to two hours by means of measuring the maternal and fetal heart rate and blood pressure acid base status plasma glucose concentration and amniotic fluid pressure During the experiments arterial blood pH and gas tensions were measured at 20 to 30 minute intervals Only one experiment was performed per day

Ritodrine hydrochloride diluted in isotonic saline was infused into either the maternal or the fetal femoral vein using precalibrated infusion pumps The dose was calculated by estimation of maternal and fetal weight and corrected by the measured weight later The weight of the ewes ranged from 45 5 to 68 0 kg and that of the fetuses from 1 1 to 4 0 kg Paired blood samples for acid base or carbohydrate metabolism measurements were obtained simultaneously from the maternal and fetal femoral arteries

Studies were performed in the following three groups

Group A Ritodrine was infused into 11 ewes in labor Uterine activity was spontaneous in eight experiments and induced with an oxytocin infusion in the other three Ritodrine was infused from 40 minutes to 4 1/2 hours at an infusion rate of 1 9 to 4 9 ug/kg/min The infusion rate of ritodrine was doubled every 20 minutes until no further decrease in uterine activity was observed Acid base studies were performed before and during the infusion

Group B Ritodrine was infused into 32 ewes not in labor at a mean constant infusion rate of 1 9 ug/kg/min for 60 minutes Arterial blood samples were obtained prior to at the end of and one hour after the ritodrine infusion Acid base plasma glucose and blood fructose lactate and pyruvate analyses were performed

Group C Ritodrine was infused into 19 fetal lambs at an increasing infusion rate until a persistent [...] was obtained The infusion rate was [...] The mean costant infusion rate was 1 9 ug/[...] 5 to 3 1 ug/kg/min) and the mean infusion ti[...]

Table I *Maternal and fetal arterial blood acid base balances and gas tensions before and during ritodrine ... sion into ewes in labor The ritodrine dose increased every 20 min from 1 9 to 4 9 µg/kg/min until no fu... inhibition of uterine activity occurred Mean values±S E*

	Before ritodrine	During ritodrine at 44 min	During ritodrine at 97 min
Maternal arterial			
pH	7 47±0 01	7 46±0 01	7 45±0 01
PO_2 (torr)	101±2	96±2	103±0 03
PCO_2 (torr)	32±1	33±1	32±1
B E (mEq/L)	0±0 5	0 5±1 0	−1 5±1 0
Fetal arterial			
pH	7 34±0 01	7 33±0 02	7 31±0 03
PO_2 (torr)	20±1	19±2	19±1
PCO_2 (torr)	49±1	50±2	50±2
B E (mEq/L)	0±1 0	0±1 5	−1 5±1 5
ΔpH	0 12±0 01	0 14±0 02	0 15±0 03
ΔB E (mEq/L)	0 5±1 0	1 0±1 5	0 5±1 0

Number of animals included in the before ritodrine during ritodrine at 44 min and during ritodrine at 97 min groups are 11 ... 10 respectively

(range 13 to 50 minutes) Arterial blood samples were obtained and analyzed as described for Group B

Analytical methods Arterial blood gas tensions and pH were measured at 39 C with Radiometer microelectrodes and base excess (B E) then calculated (16) Arterial plasma glucose was determined as the mean of five measurements using a glucose analyzer (Beckman Instruments Inc Fullerton Calif) Whole blood lactate and pyruvate concentrations were measured using the lactic dehydrogenase method (Sigma Chemica Corp St Louis Mo) Whole blood fructose was determined by the resorcinol method (22) Blood fructose lactate and pyruvate were assayed from frozen precipitates kept at −20 C in duplicate The variation coefficients were plasma glucose 3 per cent blood lactate 0 9 per cent pyruvate 7 5 per cent and fructose 15 per cent

The data were statistically evaluated by the paired t test

RESULTS

Group A The ritodrine infusion resulted in a 70 per cent decrease in uterine activity There were no significant changes in maternal or fetal arterial blood pH gas tensions or B E (Table I) Seven of the fetal lambs had a mean arterial PO_2 of 17 torr during the control period but the mild hypoxemia did not increase during the ritodrine administration

Group B When ritodrine was infused into ewes not in labor no changes were found in arterial blood pH gas tensions or B E during the infusion (Table II) One hour after completion of the infusion maternal arterial pH had increased from 7 46±0 01 to 7 48±0 01 (mean±S E) Concomitantly the pH gradient from mother to fetus increased significantly ($p<0$ 01) from 0 13±0 01 to 0 16±0 02 in the *recovery period In these experiments 22 fetal* had an arterial PO_2 of 20 torr or greater ... lambs had less than 20 torr There was no dif... between these two groups in their ... responses

Plasma glucose levels were determined in ... and 24 fetal lambs As shown in Fig 1A the ... plasma glucose was slightly elevated after one ... the ritodrine infusion and was elevated furthe... hour into the recovery period to a mean of ... mg/100 ml from a control value of 61 9 mg/... The only significant change in fetal plasma ... was an elevation from a control of 13 3 to ... mg/100 ml one hour into the recovery phase ... of the fetal lambs had an initial plasma glucose below 15 mg/100 ml and the other twelve above ... level The effect in both groups was of a ... magnitude and the combined results are reported ... observed no significant changes in blood fr... concentration in 6 ewes and their fetuses d... after the ritodrine administration (Fig 1B)

The maternal lactate concentration increased ... 8 8 to 13 5 mg/100 ml (+ 53 per cent) during the ... drine infusion and was still elevated (11 5 mg/1... one hour after the infusion (Fig 1C) Fetal lac... creased from 27 9 to 35 3 mg/100 ml (+ 27 pe... during the infusion and remained elevated ... mg/100 ml one hour later

The maternal pyruvate concentration also ... ed during the ritodrine infusion (Fig 1D) The ... tate/pyruvate ratio remained stable (3... 42 0±7 2 and 40 2±7 5) before during and ...

le II Maternal and fetal arterial blood acid base balances and gas tensions before during and one hour r ritodrine infusion into ewes in absence of uterine activity Mean dose of ritodrine was 1 9 µg/kg/min dur a mean period of 60 min Mean values±S E

	Before ritodrine	During ritodrine	After ritodrine
ernal arterial			
H	7 46±0 01	7 47±0 01	7 48±0 01
O_2 (torr)	101±2	101±2	103±1
CO_2 (torr)	32±1	31±1	31±1
E (mEq/L)	−0 5±0 5	−0 5±0 5	2 0±2 0
l arterial			
H	7 33±0 01	7 33±0 01	7 31±0 02
O_2 (torr)	21±1	20±1	ᐤ0±1
CO_2 (torr)	47±1	47±1	48±1
E (mEq/L)	−1 5±0 5	−1 0±0 5	−2 0±1 0
pH	0 13±0 01	0 14±0 01	0 16±0 02
B E (mEq/L)	1 0±0 5	2 0±1 5	2 0±1 0

ber of animals included in the before during and after ritodrine groups are 32, 32 and 28 respectively
)05 $p<0\,01$

drine infusion (mean±S E) Fetal pyruvate in sed from 1 02 to 1 23 mg/100 ml during the infu and the fetal lactate/pyruvate ratio remained hanged This effect was similar in fetal lambs with a arterial PO_2 above or below 19 torr although es without hypoxemia had lower initial levels of te and pyruvate (15 1 and 0 75 mg/100 ml res vely)

up C Ritodrine infused directly into the fetus re- d in a small but statistically significant fall in fe rterial pH (−0 01 units, $p<0\,05$) (Table III) only other significant change observed was an in e in the base excess difference between mother fetus Fourteen normoxemic fetal lambs (mean 23 torr) responded in a similar manner to five es with hypoxemia (mean PO_2 of 16 torr) No ficant changes were noted in maternal arterial base status or blood gas tensions

asma glucose measurements were made in 13 and their fetuses during the ritodrine infusions no changes were observed (Fig 2A) In 6 of these es studied in the recovery period there was a t elevation to a plasma glucose of 20 6 mg/100 from the control value of 18 mg/100 ml No rence in the responses was found between fetuses low (mean 12 7 mg/100 ml) or normal (mean mg/100 ml) glucose values

here were no significant changes in fetal or mater blood fructose with the fetal infusion of ritodrine 2B)

oth lactate and pyruvate concentrations increased ng the fetal ritodrine infusions (Fig 2 C & D) These changes were similar in six normoxemic fetuses and in three hypoxemic fetuses The lactate/pyruvate ratio was 20 0±1 6 during the control period 19 4±2 9 during the infusion and 20 2±3 2 one hour into the recovery period (mean±S E) Maternal lac tate and pyruvate concentrations remained unchang ed

DISCUSSION

The acid base balance of the ewe and her fetus under went no major alterations during the infusion of rito- drine either into the ewe or the fetus Although ma ternal arterial lactate and pyruvate levels were in creased this was not reflected in any major change in maternal arterial pH or PCO

While maternal pH is dependent on respiration metabolic changes and accumulation of organic acids the fetal acid base balance is also influenced by changes in uterine and umbilical blood flow We have previously demonstrated that ritodrine infusions in doses similar to those used in the present studies cause no major change in uterine or umbilical blood flow in sheep (18 19) The accumulation of organic acids may play a role in decreasing fetal arterial pH However although the decrease in fetal arterial pH was statistically significant the magnitude of the decrease was only 0 01 pH units These findings are in accord with other studies where a 31±7 per cent (mean±S E) reduction in uterine blood flow assoc iated with a ritodrine infusion rate of 800 ug/min for two hours elicited no significant changes in maternal or fetal arterial pH PCO or PO (7)

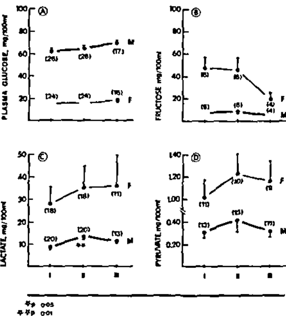


Fig 1 Maternal and fetal arterial plasma glucose (A) blood fructose (B) blood lactate (C) and pyruvate (D) levels before (I) during (II) and one hour after (III) ritodrine infusion into the ewe Ritodrine dose 1 9 ug/kg/min duration of infusion 60 min Mean values±S E Number of animals indicated in parenthesis M=mother F=fetus

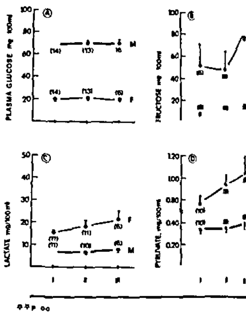


Fig 2 Fetal and maternal arterial plasma glucose (A) fructose (B) blood lactate (C) and pyruvate (D) before (I) during (II) and one hour after (III) ritodrine infusion into the fetal lamb Ritodrine dose 1 9 ug/ duration of infusion 29 min Mean values ±S E N animals indicated in parenthesis M=mother F

It has been suggested from studies in humans that the use of ritodrine during labor may improve fetal pH and base excess values (10 8) In the present investigations in sheep we were unable to demonstrate any improvement in fetal arterial pH or blood gas tensions with inhibition of uterine activity with ritodrine

Both arterial lactate and pyruvate concentrations in the ewe and the fetal lamb were elevated during the ritodrine infusion and tended to remain elevated for at least one hour after cessation of the infusions The stable lactate/pyruvate ratios in mother and fetus indicate that the ritodrine infusions stimulated both aerobic and anaerobic glycolysis Furthermore the response of the hypoxemic fetal lambs was similar to the normoxemic lambs even though the initial lactate levels were higher in the hypoxemic group

It has previously been demonstrated that lactate may serve as an important substrate for fetal metabolism (4 6) and that lactate may be derived from placental conversion of glucose (4) The present studies in which there was a relatively small elevation of fetal plasma glucose compared to the more pronounced increases in fetal arterial lactate could be interpreted as an increase in fetal glycolysis due to the ritodrine infusion It remains to be whether the increased fetal lactate served during beta adrenergic stimulation dary to placental conversion or due to cogenolysis and to what extent the by the fetus

The maternal and fetal plasma glucose only moderately elevated during the mater drine infusion at the doses used These agreement with other studies using similar rates (7) The fetal infusion resulted in on elevation in plasma glucose in the recover previous studies infusion rates two to four ones we utilized have been reported to result in icant increases in plasma glucose values from glycemic values (8 mg/100 ml) (7) It is quite po that with higher infusion rates of ritodrine longer duration there could be a more sig elevation of fetal plasma glucose levels

Human studies have indicated that hypo of the newborn is rarely seen following th ritodrine (1) That the beta adrenergic system the regulation of glucose homeostasis has al demonstrated by the hypoglycemia reported use of beta adrenergic blocking agents (17) L

le III *Maternal and fetal arterial blood acid base balances and gas tensions before during and one hour* ·ritodrine infusion into fetal lambs Mean dose of ritodrine was 1 9 µg/kg/min during a mean period of 29 *Mean values±S E*

	Before ritodrine	During ritodrine	After ritodrine
·rnal arterial			
I	7 48±0 01	7 49±0 01	7 50±0 01
)$_2$ (torr)	102±3	101±2	101±2
˙O$_2$ (torr)	30±1	32±1	31±1
E (mEq/L)	0±0 5	1 0±1 0	1 5±0 5
l arterial			
I	7 36±0 01	7 35±0 01	7 34±0 01
)$_2$ (torr)	21±1	21±1	20±1
O$_2$ (torr)	44±1	44±1	46±2
E (mEq/L)	− 1 0±0 5	− 1 5±1 0	− 1 0±1 0
›H	0 12±0 01	0 14±0 01	0 15±0 01
3 E (mEq/L)	0±1 0	2 5±1 0	3 0±1 0

›er of animals included in the before during and after ritodrine groups are 16 15 and 13 respecti ely for mother and 19 19 and etus

I 05

.d glucose and lactate in fetal lambs subjected to ·rnal hypoxemia or epinephrine infusion into the ˜ have also been reported (15) Thus it is possible ritodrine may assist in the response of the fetus ress in averting hypoglycemia However a study e effects of prolonged administration of the drug dicated in order to ascertain whether glycogen ;s could be depleted and thus potentially rsely affect the response of the fetus

ucocorticoid administration in rabbits has been 'm to increase glucose incorporation into phos idyl choline by promoting glycogenolysis (11) observation plus the r lease of free fatty acids ıg beta adrenergic stimulation (21 13) may be a between the reported decreased incidence of ratory distress syndrome and the use of beta ad rgic drugs

immary the ritodrine infusions resulted in mater ınd fetal metabolic changes similar to those seen ng stress but without resulting in any adverse base balance changes It remains to be idated to what extent the fetus is able to utilize increased metabolic products of carbohydrate ıbolism

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APPENDIX

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The papaer has been presented in part at the [illegible] Meeting of the Society for Gynecologic Investigation[illegible]

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SHORT COMMUNICATION

THE USE OF PULSED HIGH FREQUENCY THERAPY (CURAPULS) IN GYNECOLOGY AND OBSTETRICS

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curapuls device can be used to give both ultra t wave diathermy and athermic pulsed high fre icy therapy The biological effects of the latter be regarded as the same as those of ultrashort diathermy with the difference that no continu elevation of temperature ensues (2) We investi l earlier the effect of pulsed high frequency ipy on vulval epithelial lesions and noted a bene l effect in most cases (1) We have now studied ised of curapuls in other gynecological and also tric indications

IJECTS AND THE MODE OF TREATMENT

puls therapy was administered to 71 gynecological pa whose mean age was 44 2 years (range 19–72) The patients were classified by diagnosis Table I d high frequency therapy in cycles of 10–15 single nents at intervals of two days was administered using urapuls device A pulse repetition frequency of 62 Hz 300 W was used The patients were examined before uraputs therapy and two weeks after treatment rthermore we studied the effect of pulsed high fre y therapy on involution of the uterus after cesarean in in five women the size of the uterus being ured by means of ultrasound and compared these five control patients who received no therapy

RESULTS AND DISCUSSION

The diagnoses and the changes occurring in the pa tients symptoms during pulsed high frequency therapy are presented in Table I The response to therapy appears to have been good in parametropathy eight of 10 patients were either symptomless or had improved following therapy The symptoms of most of the patients in the other groups with the ex ception of endometriosis had also either disappeared or diminished during treatment

No significant differences were demonstrated in in volution of the uterus after Caesarean section be tween the patients given pulsed high frequency therapy and the control group

Pulsed high frequency therapy appears to have a beneficial effect in various painful conditions located to the pelvic region Good results were achieved in the treatment of spastic parametropathy a condition characterized by troublesome lower abdominal and lumbosacral pain where the parametria are tense and tender This painful condition is often of long dura tion and resistant to spasmolytics and other medica tion Curapuls therapy appeared to exert a favorable action also in postoperative conditions The possible effect of high frequency therapy on the scar forma tion of the Caesarean section wound must be left to future studies

e I *Patients treated by pulsed high frequency therapy*

nosis	Total	Symptomless	Better	Unchanged
tic parametropathy	10	6	2	2
bago	9	3	5	1
ometriosis	5	–	2	3
operative status	16	9	4	3
radiotherapeutic status	8	2	4	2
er abdominal pain (cause unknown)	23	10	9	4
l	71	30	26	15

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SHORT COMMUNICATION

THE EFFECT OF CERVICAL ENCERCLARGE ON UTERINE DIMENSIONS

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act Observation of women who underwent cerclage uterine cervix in pregnancy indicated that during the 24 hours after operation a marked increase of the e size takes place
ce this feature came rather as a surprise seventy one were studied carefully

MATERIAL AND METHODS

ty-one patients of gestational ages 12 – 17 weeks who treated or incompetence of the internal cervical os at on Government Hospital Jaffa during the period November 1976 through August 1979 were investigat

cerclage was carried out according to the method sed by McDonald (1957) A single tobacco-pouch was placed approximately one cm below the inter rvical os Under general anesthesia a purse string cir ture of silk n 3 carried on a Mayo needle was in taking four bites of cervical tissue

t prior to the operation the urinary bladder was emp- with the patient in lithotomy position The upper n of the symphysis pubis and the border of the uterine s were throughly palpated and marked with a dye on the abdominal skin The midline distance between the two lines was measured in cm and recorded

The same procedure was repeated 24 hours after opera tion All the measurements were carried out by the same doctor In twenty five cases the height of the uterine fundus was measured and recorded independently by two doctors and the results compared Differences in the measurements recorded by the two independent doctors were not signifi cantly

All patients were kept in bed for 24 hours after the opera tion i e until the second measurement had been carried out To exclude the possibility of the results obtained in the study group being due to the bed rest alone measurements of uterine height were carried out in a control group of women of similar gestational ages who did not undergo cerclage In the control group a 24-hour period of bed rest did not cause any change in the height of the uterine fundus

In ten cases an attempt was made to measure the sizes of the uterine cavity and the thickness of the uterine wall using ultrasonography but we were unable to obtain accurate measurements because of the difficulty of identifying the same uterine plane in the repeat examination The results suggested however that the size of the uterine cavity itself remained unchanged after the operation

Twenty-one women were checked independently a fort night later and the expected and actual uterine sizes cor responded

1 *Mean differences in uterine size before and after cerclage*

			Mean distance between symphysis pubis and uterine fundus (cm)		
of patients	Parity	Gestational age (in weeks)	before cerclage	24 hours after cerclage	mean difference (cm)
	0 – 3	12	8 84	11	2 16
	0 – 3	13	9 79	11 97	2 17
	0 – 4	14	8 78	10 92	2 14
	2 – 3	15	9 2	10 79	1 59
	2	16	10	12	2
	1	17	10 25	12	1 75

RESULTS

The size of the uterus following cerclage as measured by the distance between the symphysis pubis and the upper board of the uterus was increased in all 71 patients (Table I) The mean increase was 1 97 cm S D ±0 22 cm The median increase was 2 cm The postoperative increase in the height of the uterine fundus was not dependent on the pre operative size No correlation was found between the degree of the post cerclage uterine enlargement ' and the gestational age or parity of the mother

COMMENTS

Recent work (Bibby *et al* 1979) has demonstrated that during the early part of the second trimester of pregnancy cervical encerclarge is associated with a rapid significant rise of 13 14 dihydro 15 keto prostaglandin F (PGFM) which reflects an increase in intra uterine production of prostaglandin $F_{2\alpha}$ which in turn is known to influence capilary permeability (Vane 1971)

Since ultrasonographic investigation indic[illegible] change in the size of the uterine cavity [illegible] that the increase in height of the uterine fu[illegible] lowing cerclarge is due to a thickening of th[illegible] wall resulting from congestion

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LETTER TO THE EDITOR

STATISTICAL COMPARISON IN A CONTROLLED TRIAL OF ELECTIVE INDUCTION OF LABOR

r Sir

leskär *et al* (2) recently reported some findings a prospective randomized study on induced ver pontaneous labor dealing with the effects on the her and the fetus They concluded that given head entation normal pregnancy and careful selection atients with respect to the length of pregnancy the condition of the cervix induction of labor us the Cardiff Infusion System with intrauterine ure recordings and continuous fetal heart rate itoring is not associated with any increased risks he mother or fetus during labor and delivery

ie authors based their conclusions on statistical applied to a variety of outcomes where no sig ant differences were found They reported mean s standard deviations and p-values for their urements and tests on the varied outcomes In r words they reported on the probabilities of dis ring differences between the two groups when in fact are none However nowhere in the r do the authors discuss the possibility of over ing a real differenece between the two groups

e think this is a crucial omission particularly in es like the one under discussion where the ors conclude that there are no differences be n the two groups Unfortunately this type of in ation is too often missing in similar reports (1)

order to illustrate the importance of these con ations we shall take a closer look at a few of the ings reported by Tylleskär *et al*

ie analysis is based on comparison of variable omes for 84 women 43 with induced labor and lelivered spontaneously We shall focus on two parisons reported in Tables IV and VI in their r and will restrict our discussion to the findings rted for primiparae

iparison 1 concerned uterine activity at 6 cm cer l dilatation expressed in Montevideo units which the induction group of 20 cases was found to be ±58 and for 15 of the spontaneous group 152±51

Comparison 2 concerned the amount of bleeding in ml during the third stage of labor which for the two groups was 376±216 and 332±242 respectively

For both these comparisons the authors concluded that there were no statistically significant differences between the induced and the spontaneous groups

We have computed the chances of concluding that there is no difference between the two groups when in fact there is a real difference and have related these chances to the magnitudes of such true differences These relationships are shown in Table I

From the table it is seen that in the reported study with a chosen significance level of 0 01 there is a 50 per cent chance of wrongly concluding that there is no difference between the groups even if there were a real difference in uterince activity of 47 Montevid eo units (31 per cent of the observed mean value in the spontaneous group) and a real difference in bleeding of 183 ml (54 per cent of the mean value in the spontaneous group) In order to have only a 10 per cent chance of making similar mistake the true differences have to be at least 72 Montevideo units and 282 ml respectively The corresponding differ

Table I *Probability of wrongly postulating no dif ference for the sample sizes and results presented by Tylleskär et al* (2)

	Probability			
	0 10	0 25	0 50	0 75
Comparison I				
Uterine activity (M U)				
Sign level p<0 01	72	61	47	32
Sign level p<0 05	58	45	32	20
Comparison II				
Bleeding (ml)				
Sign level p<0 01	282	236	183	126
Sign level p<0 05	225	175	126	76

ences are somewhat reduced if one decides on a significance level of 0 05

This discussion can of course be extended to all the other results in which no significant differences were found

This should make it abundantly clear how cautious one should be when discussing the findings and drawing conclusions based on relatively small scale studies even though they may be carefully designed and conducted

We think it is urgent to stress this fact and to encourage authors to include in the discussion of their findings considerations of the type mentioned here

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DURATION OF THE SECOND STAGE OF LABOR

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m the Department of Obstetrics and Gynecology Akershus Central Hospital University of Oslo School of Medicine and the Department of Obstetrics and Gynecology Gjøvik Hospital Gjøvik Norway

tract The second stage of labor defined as the time n full dilatation of the external os to delivery of the 3 was recorded during a three month period in 635 la with vaginal delivery The median duration in labors of ıtaneous onset was 31 3 minutes in para 0 mothers 14 3 utes in para 1 mothers and 11 7 minutes in para 2+ hers In induced labors the second stage had approxi ly the same length as in labors with spontaneous onset time distribution showed that the second stage in para 0 hers had a plateau in the 17 5–37 5 minute range reas para 1+ mothers had a sharper peak at 7.5 min Forty and 45 minutes respectively seemed to be limits ond which only very few second stages of labor lasted rative delivery terminated 18 per cent of para 0 labors 6 per cent of the para 1+ labors entering the second The operative interventions seemed to appear in two ers for each parity group It appeared that fetal asphyx quiring intervention was discovered before 40 minutes ie second stage in para 0 and before 30 minutes in para mothers Later operative termination was more often ormed to relieve fatigued mothers

ı previous study from Akershus Central Hospital median duration of labor with spontaneous onset found to be 8 hours 14 minutes for para 0 4 rs 30 minutes for para 1 and 4 hours 49 minutes para 2+ women The second stage defined as the e from full dilatation of the external os to delivery he child accounted for 16 10 and 8 minutes of ›e durations respectively (2) The data were ana d by using electronic processing of information tinely collected through specially designed parto-ms (1) On the partograms the key measurements the process of labor were marked to the nearest ırter of an hour except for the time of delivery ıch was exact While the results are undoubtedly ıd where the total duration of labor and its first ge are concerned the rounding error may have sed the duration of the second stage Three current ındinavian textbooks of obstetrics give widely dif ent figures for the average duration of the second ge of labor in nullipara varying from 0 5 to 3 hours (3 4 5) To obtain a better estimate of the true dura tion of the second stage of labor we designed the fol lowing study

MATERIAL AND METHODS

The study took place during three months from January to April 1978 For every birth the length of the second stage of labor was specially recorded from the time of a fully dilated cervix to the delivery of the child or children Other relevant information such as spontaneous or induced labor epidur al analgesia fetal presentation operative delivery weight of the newborn and Apgar score was also noted on special forms which were filled in by the midwives

The two participating hospitals were Akershus Central Hospital (ACH) and Gjøvik Hospital (GH) The obstetrical department of ACH has three senior and 9 junior doctors while the staff at GH has two gynecologists for which reason collaboration with the surgical department is neces sary Uncomplicated labors and deliveries are handled by midwives in both hospitals

The total number of births during the study was 183 at GH and 531 at ACH (Table I) Of these 60 were cesarean sections with no second stage of labor and 7 twin births which were excluded from this study Table I shows that the proportion of cesarean sections was higher at GH than at ACH (11 5 against 7 3 per cent) and that the difference was due to more frequent use of cesarean sections during labor at GH the percentages of elective operations being equal

In twelve cases the length of the second stage was not re corded This was due to heavy work load and we do not think that the omission of these cases has biased the results The analysis comprises 635 labors of which 243 (38 3 per cent) were in primipara (para 0) and 392 (61 7 per cent) in mothers who had given birth before (para 1+) Labor was induced by oxytocin in 91 (14 3 per cent) the rest being la bors with spontaneous onset

The type and frequency of operative intervention during the second stage of labor are shown in Table II Labor ter minated spontaneously in 82 3 per cent of para 0 and in 94 4 per cent of para 1+ mothers In the study group there were no cases of fetal death before the onset of labor

In presenting the findings of the study the results are be ing pooled However separate analysis of data from the two hospitals revealed no differences in any of the parame ters studies

Table I *Births during study period 16th January – 15th April 1978*

	Gjøvik Hospital		Akershus Central Hospital		Both institutions	
	No	%	No	%	No	%
Second stage recorded	157	85 5	478	90 0	635	88 9
Second stage completed but not recorded	2	1 1	10	1 9	12	1 7
Cesarean section during first stage	13	7 1	15	2 8	28	3 9
Cesarean section elective	8	4 4	24	4 5	32	4 5
Twin births not recorded	3	1 6	4	0 8	7	1 0
Total	183	100 0	531	100 0	714	100 0

RESULTS

The average duration of the second stage of labor is shown in Table III It is seen that the second stage lasts about 30 minutes in para 0 mothers both for labors of spontaneous and non spontaneous onset In mothers who had given birth previously (para 1+) the duration was about 15 minutes or half that in mothers who had their first delivery In labors with spontaneous onset para 2+ mothers had slightly shorter second stage than para 1 mothers 11 7 minutes and 14 3 minutes median duration respectively In induced labors the number of para 2+ mothers was very small and did not allow for separate analysis

By studying the distribution of the length of the second stage of labor in spontaneous and induced labors no noticeable difference was found neither in para 0 nor in para 1+ mothers The cumulative and frequency distributions are therefore shown together for spontaneous and induced labors in Fig 1 As shown in the figure the bulk of para 0 mothers have a second stage length of between 15 and 40 minutes while para 1+ mothers have a sharper peak in [illegible] terval 5 to 10 minutes Very few second stage[illegible] longer than 45 minutes particularly in pa[illegible] mothers The longest duration of the second st[illegible] corded in this study was 107 minutes for on[illegible] mother and 70 minutes for a para 1+ mothe[illegible] visualizes the point made by Table III that th[illegible] duration of the second stage is slightly longer th[illegible] median duration This is due to the skewed f[illegible] distributions with long tails to the right

The distribution of operative interventions [illegible] the second stage by time interval showed two [illegible] peaks for both para 0 and for para 1+ mo[illegible] seen in Table IV The first peak of interventio[illegible] tween 10 and 40 minutes in para 0 and before [illegible] utes in para 1+ mothers is thought to refle[illegible] distress whereas the second peak at 50+ [illegible] reflects exhausted mothers with prolonged [illegible] stages This assumption is being supported by d[illegible] tribution of low Apgar scores which had a pe[illegible] responding to the first intervention peak b[illegible] para 0 and para 1+ mothers

Table II *Incidence of intervention in the case study by parity*

	Para 0		Para 1+	
Type of intervention	No	%	No	%
None	200	82 3	370	94 4
Vacuum extraction	26	10 7	17	4 3
Forceps	13	5 4	2	0 5
Cesarean section	3	1 2	0	0
Assisted breech	1	0 4	3	0 8
Total	243	100 0	392	100 0

Table III *Average duration of the second stage of labor (minutes) by onset of labor and by parity*

			Average duration	
Onset of labor	Parity	No	Median	[illegible]
Spontaneous	Para 0	213	31 3	[illegible]
	Para 1	245	14 3	[illegible]
	Para 2+	86	11 7	[illegible]
Induced	Para 0	30	[illegible]7 5	[illegible]
	Para 1+	61	14 4	[illegible]

average duration in minutes

e IV *Distribution of interventions during the second stage of labor by time interval and by parity*

of cases	Time interval from beginning of second stage (minutes in per cent) 0–9	10–19	20–29	30–39	40–49	50–59	60+	Total
Para 0	–	16 3	11 6	18 6	–	14 0	39 5	100 0
Para 1+	13 6	18 2	22 7	9 1	9 1	13 6	13 6	100 0

was considered to be of interest to e if the dura the second stage of labor can be predicted by otal duration of labor For para 0 mothers there a slight but definite correlation between these parameters the coefficient of correlation being ·34 For para 1+ mothers the coefficient of cor non was close to zero (r = 0 0529)

e length of the second stage of labor was also ed in relation to the birth weight of the child hildren weighing less than 3 000 grams there was ht tendency towards a shorter second stage

DISCUSSION

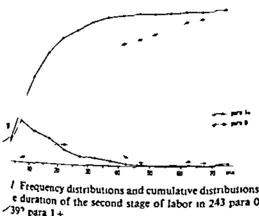
length of the second stage of labor is in many in es determined by operative intervention This he case with 17 7 per cent of para 0 mothers and er cent of para 1+ mothers in this study Some ve cesarean sections were performed in cases e a prolonged second stage may be anticipated to such interferences a true biological picture of econd stage cannot be obtained The error intro d by operative deliveries is mainly a shortening of the mean values in Table III The median values which give the time when 50 per cent have completed the second stage will however be less affected

We found the second stage of labor to last some what longer than in the previous computer based study on the duration of each stage of labor (2) The probable reason for this discrepancy is the rounding error previously mentioned The average lengths found about 30 minutes for para 0 and 15 minutes for para 1+ mothers are still low in relation to state ments in two of the quoted textbooks (3 4)

The time-distribution curves for para 0 and para 1+ mothers (Fig 1) were different in shape Para 0 mothers had a long flat plateau in the 17 5–37 5 minute range while para 1+ mothers showed a peak at 7 5 minutes followed by a smooth fall Forty and 45 minutes seemed to represent limits beyond which only very few second stages lasted

Operative interventions in the second stage of labor seemed to appear in two different clusters for each parity group The data sets were small however both groups showed the same pattern When this was cou pled with the distribution of low Apgar scores (not tabulated) it appeared that fetal asphyxia requiring intervention was discovered before 40 minutes in para 0 and before 30 minutes in para 1+ labors Operative termination beyond these limits was more often per formed to relieve fatigued mothers

The second stage of labor is the period of greatest physical strain on both mother and fetus Operative delivery upon signs of life threatening fetal asphyxia is mandatory In Norway it is our impression that the attitude in many maternity institutions in prolonged second stages with no signs of fetal asphyxia is to wait and see This may have profound ill-effects on the mothers who in many cases look back upon their labors as a shocking experience which they never want to repeat The question of when to intervene in prolonged labor can be resolved on the basis of the time-distribution graphs of the second stage It appears that 45 and 35 minutes are reasonable limits in para 0 and para 1+ labors respectively



1 Frequency distributions and cumulative distributions e duration of the second stage of labor in 243 para 0 39? para 1+

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TABOLIC EFFECTS OF INTRAVENOUS RITODRINE INFUSION IN PREGNANCY

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·r The effects of intravenous administration of ne on blood glucose insulin electrolytes plasma l cell potassium and venous pH were investigated ;hly significant increase in blood glucose and insulin d A highly significant negative correlation between ind red cell potassium concentration was registered ·96 68)
ignificant changes during Ritodrine infusion were d in serum levels of sodium chloride calcium phos and magnesium
pH did not seem to be influenced by intravenous ne administration
ardiac arrhythmias or electrocardiographic deterio- occurred
e intravenous Ritodrine administration seems to be normal pregnancies a risk may be present in diabetic ,italized patients and pregnant women being treated etics

ine a potent beta adrenergic agent is being icreasingly in obstetrics to supress uterine con ns in the management of premature labor (2 8

iough the metabolic effects of this drug have :en thoroughly evaluated constant findings of :on in blood glucose and insulin levels and ise in serum potassium during intravenous Rito administration have been reported (3 6 7 13) ' purpose of this investigation was to determine nical and metabolic effects of intravenous infu f Ritodrine Specially correlations between ma carbohydrate metabolism ionic equilibrium of ium and electrocardiographic findings were in ated

MATERIAL AND METHODS

:lected group consisted of ten patients considered at ' premature labor because of previous preterm deliver :h or without cervical incompetence placenta previa mature uterine contractions Patients with a familial t history of diabetes mellitus were not included in the

The charcteristics of the patient population are shown in Table 1

Normal saline infusion was begun via a scalp vein set at 8 a m at a rate of 1 ml/min blood samples were collected from the collateral antecubital vein both at the beginning of the infusion and after 30 and 60 minutes After one hour Ritodrine was administered by an infusion pump at a cons tant rate of 200 μg/min Blood samples were collected at 30 60 120 and 180 minutes during the Ritodrine infusion The samples were divided with one part immediately serving to measure glucose (Technicon Auto-Anal N16b) electrolytes (Eppendorf flame photometry) and potassium levels in erythrocytes Red cell potassium was calculated according to the following formula

$$K_{RBC} = \frac{K_H \; K_p \; (1-Htc)}{Htc}$$

where K_{RBC} = potassium concentration in red blood cells K_H = potassium concentration in hemolysate K_p = potassium concentration in plasma and Htc = hematocrit

Hemolysis was achieved by adding two parts of distilled water to one part of whole blood

The other part of each sample was stored in deep freezer at 20 C for insulin assay by RIA method (Sorin France)

Heparinized blood samples were immediately analyzed for pH values (Radiomether Copenhagen BMS3 MK)

Urine collected before and after the second and fourth hour of infusion was analyzed for potassium (Atomic absorption spectrophotometer Techtron M 1 00) and creatinine (Jaffy reaction)

Pulse rate and blood pressure were measured after each blood sample collection and electrocardiograms were performed in all patients at time 0 and during the third hour of Ritodrine infusion

In all patients blood glucose insulin serum and erythrocyte potassium levels were again determined ~0 hours after the infusion

Table I *Characteristics of patient population*

Number of patients	10
Age (in years)	23 8±4 8
Nulliparae	4
Primiparae	6
Singleton pregnancy	8
Twin pregnancy	~
Weeks of gestation	30 6±2 8

Table II *Mean values and standard deviations (mmol/l and pH units respectively) of the parameters investigated during saline and ritodrine administration Time in minutes before and after 0 time*

	−60	−30	0	+30	+60	+120	+1[illegible]
Glucose	4 12±0 41	4 13±0 2[illegible]	4 0[illegible]±0 31	4 70±0 46	5 22±0 56	5 61 0 36	[illegible]
Insulin	88 2 ±37 6	93 2 ±28 4	96 8 ±[illegible]9 4	205 9 ±59 5	253 3 ±7 5	[illegible]30 3 ±63 5	[illegible]
K_S	3 7[illegible]±0 39	3 65±0 3[illegible]	3 65±0 37	3 17±0 42	2 85±0 37	2 73 0 34	[illegible]
K_{RBC}	91 7 ±[illegible] 67	91 9 ±2 40	91 9 ±[illegible] 77	93 2 ±2 95	93 9 ±1 96	93 8 ±2 14	[illegible]
Na	141 0 ±2 65	140 0 ±3 [illegible]6	140 2 ±3 48	140 4 ±3 9[illegible]	141 7 ±2 45	141 2 ±4 54	[illegible]
Cl	101 [illegible] ±3 6	99 8 ±3 [illegible]	100 8 ±3 8	99 8 ±3 4	101 2 ±3 8	101 8 ±3 6	[illegible]
Ca	2 24±0 12	2 20 0 10	2 24±0 11	2 20±0 15	2 19±0 12	2 16 0 12	[illegible]
Ph	1 07±0 31	0 97±0 21	0 97±0 18	0 91±0 20	0 96±0 27	0 93 0 16	[illegible]
Mg	0 85±0 19	0 86±0 19	0 85±0 15	0 84±0 15	0 76±0 24	0 75 0 16	[illegible]
pH	7 28±0 06	7 29±0 03	7 32±0 03	7 30±0 05	7 30±0 06	7 [illegible]9 0 10	[illegible]

RESULTS

The mean values and standard deviations of all the parameters which were investigated are presented in Table II

Blood glucose values were not influenced by saline infusion however they rose significantly during Ritodrine infusion from a mean value of 4 12 mmol/l to 5 91 mmol/l (Fig 1) $t<0\ 005$ in all instances Blood glucose levels taken 20 hours thereafter returned to preinfusion values (4 16 mg/dl)

Blood insulin levels were significantly increased 30 and 60 minutes after Ritodrine infusion ($t<0\ 005$) thereafter an insignificant decrease in insulinemia occurred (Fig 2)

Serum potassium exhibited a highly sign[illegible] during the first hour of Ritodrine adm[illegible] compared to the levels during saline [illegible] ($t<0\ 005$) a less significant fall continuing [illegible] ($t<0\ 025$) The difference in serum potass[illegible] that estimated at the beginning and again [illegible] mination of Ritodrine infusion was 1 08 mmol[illegible] 3) Serum potassium measured after 20 hours [illegible] levels similar to preinfusion values (3 7[illegible] mmol/l) Red cell potassium levels were not [illegible] ed by saline infusion During the first hour [illegible]



Fig 1 Glycemia mean ± SD during saline and ritodrine infusion

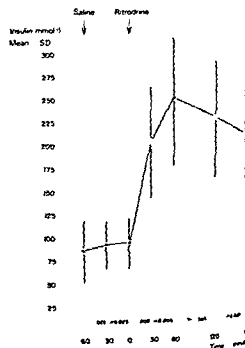
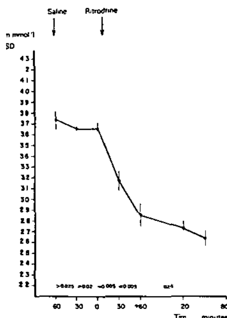


Fig 2 Insulinemia mean ± SD during saline and ri[illegible] administration



! Potassium levels mean ± SD during saline and rine infusion

infusion red cell potassium showed a highly ficant rise (t<0 005) thereafter an insignificant ease being observed (Fig 4) The correlation co- ient between plasma and red cell potassium was ly significant (r = −0 962) (Fig 5)

milarly a highly significant negative correlation found between serum glucose and potassium lev while a positive correlation (r = +0 983) was re red between insulinemia and red cell potassium entration

he other ions investigated were sodium cloride um phosphorus and magnesium No influence hese parameters was noted by saline or by Rito- e infusion The venous pH was not influenced ng saline or Ritodrine infusion

o significant difference in the urinary potassium tinine ration was found

linically an increase in the heart rate was stered in all patients No arrhythmias or altera s in the ECG were observed

DISCUSSION

amimetics activate adenylate cyclase an enzyme ich catalizes the conversion of ATP to cyclic IP resulting in an accumulation of intracellular lic AMP (10) Cyclic AMP both activates hepatic glycogen phosphatase and inactivates glycogen syn thetase resulting in an increased output of glucose from the liver (5)

Blood insulin elevation occurs probably as a result of the cyclic AMP mediated stimulating effect on the pancreatic beta cells (1 9) and as a result of an in direct influence due to the elevated blood glucose lev els

While the observed elevation in blood glucose seems not to be a risk in normal patients with an ade quate pancreatic reserve such changes assume impor tance in the diabetic patients Three cases of diabetic pregnant women treated with Ritodrine showed a sig nificant increase in insulin requirement during the in fusion (4 14)

Previous investigation has found that serum potas sium *drops abruptly during Ritodrine infusion* (7) This hypokalemic action of Ritodrine may be secon dary to an elevated blood glucose and the increased insulin secretion however we have been unable to find any data concerning the metabolic fate of the po- tassium lost actively from the plasma space The pres ent study correlates the elevated red cell potassium levels with lowe ed serum levels suggesting that po- tassium lost to the plasma space actively enters the erythrocyte compartment

In the average pregnant woman in the third trimes ter the total plasma volume would amount to 4 000 ml and the red cell volume would be approximately

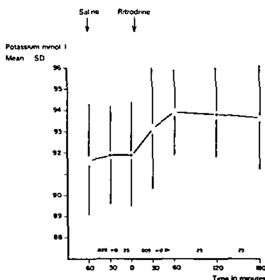


Fig 4 Potassium concentration in red blood cells mean ± SD during saline and ritodrine infusion

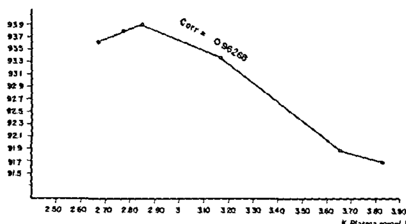


Fig 5 Correlation coe between plasma and re potassium levels

1 800 ml (12) With the mean maximal drop in serum potassium taken as 1 mmol/l the average total loss of potassium from the plasma space would be 4 mmol On the basis taking the average maximal increase in red cell potassium (1 9 mmol/l) the total gain of potassium to the red cell space would amount to a very similar quantity of 3 42 mmol This would suggest that the potassium loss from the plasma space under Ritodrine infusion could be accounted for by migration into the red cells

As indicated above our results did not show any clear cut alteration in urinary potassium during Ritodrine infusion a finding which precludes enhanced urinary excretion as a cause for the observed decrease in serum potassium levels

To our knowledge this is the first report indicating a dynamic and reciprocal increase in red cell potassium in the presence of a decreasing serum potassium under the effect of Ritodrine infusion Both serum and red cell potassium concentrations were found to be at preinfusion levels 20 hours following its termination Information is lacking concerning the dynamic behavior of both these parameters during the period following the infusion

The acute and significant hypokalemia manifested during Ritodrine infusion may be of great clinical importance in some selected cases such as in digitalized patients where it may result in deleterious effects Another clinical situation which deserves special attention under such conditions is represented by patients treated with diuretics In these cases Ritodrine infusion may be superimposed on an established hypokalemic state increasing the hazard of a severe acute hypokalemia

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A COMPARISON OF THE ANALGESIC EFFECTS OF METHOXYFLURANE NITROUS OXIDE AND NITROUS OXIDE ALONE DURING LABOUR RELATED TO THE EYSENCK PERSONALITY INVENTORY TEST

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tract One hundred and thirty three parturients who had ived either methoxyflurane nitrous oxide or nitrous ox analgesia with or without pudendal block underwent Eysenck Personality Inventory Test on the second post um day and evaluated their memory of the pain (Sub-ively Evaluated Pain Suffering Scores) during labor turients who had received methoxyflurane nitrous oxide lgesia reported significantly lower pain suffering than urients who had had nitrous oxide analgesia

ubdivision according to Personality Inventory factors wed that at the introvert end of the Extroversion Intro-ion scale methoxyflurane nitrous oxide analgesia with nithout additional pudendal block resulted in significant ower pain suffering than did nitrous oxide analgesia On other hand nitrous oxide analgesia without additional endal block gave significantly lower pain suffering at extrovert end of the scale

mong the extroverts there was a tendency though not istically significant towards non approval of the puden block

re are many favourable reports on the analgesic cts of methoxyflurane alone or in combination h nitrous oxide (2 5 6 11 13 14) However ne of these reports considered differences in per ality when evaluating the differences in analgesic ct

The purpose of the present study was to look for ferences in analgesic effect between the combina n of methoxyflurane and nitrous oxide and nitrous de alone during labour and to relate the findings results of the Eysenck Personality Inventory test PI) (7)

MATERIAL AND METHODS

e hundred and thirty three parturients were studied thoxyflurane nitrous oxide-oxygen analgesia or nitrous de-oxygen analgesia was given during alternating three ek periods Pudendal block was added by the midwives en found necessary

The parturients received either

a) Nitrous oxide 70 per cent in oxygen from a Dedolator (AGA) (n = 28)
b) Method a) supplemented with pudendal block anesthe sia (n = 21)
c) Methoxyflurane 0 1 – 0 3 per cent from a Cyprane vapourizer in 50 per cent nitrous oxide in oxygen from a Juno Mark II analgesia apparatus (Mediada) (6) (n = 37)
d) Method c) supplemented with pudendal block anesthe sia (n = 47)

All parturients in the study received 50 mg Atarax[R] (Hydroxyzine) and 50 mg Pethidine intramuscularly before the start of inhalation analgesia in accordance with the routine at our clinic No other drugs were used Inhalation analgesia was started when the cervix had dilated 4 – 5 cm in primigravidae and 3 – 4 cm in parous women Pudendal block was performed by the midwives using a Kobac needle and 1 per cent mepivacaine solution (Carbocaine[R]) Pudendal block was deemed successful when the parturient experienced anesthesia in the perineal region There were no significant differences between the four analgesia groups with respect to age and parity

On the second postpartum day the parturients were submitted to the Eysenck Personality Inventory Test (7) analyzed by a psychologist (I Å) from the Psychiatric clinic of the University Hospital On the same occasion the parturient assessed her memory of the pain suffered during labour by putting a mark on a vert cal line between two points no pain (0 scores) and unbearable pain (100 scores) This test was conducted by a test leader who only handed the papers to the parturient and instructed her The test leader did not know the type of analgesia used during labour and did not evaluate the results

A rather crude estimation of the course of labour was done retrospectively by one of the authors (B E D) according to criteria shown in Table I The course was graded so that a short uncomplicated normal delivery received a score of 0 and a long labour complicated by vacuum extraction and episiotomy or anal sphincter rupture received a high score (maximum 17)

All statistical calculations were performed according to least square methods (Student s t test analysis of variance analysis of regression) Weighted means were calculated using standardized weights

Table I *Medical assessment of the difficulty of the labor*

Stage			Score
Stage 1	Cervical dilation 2–5 cm	0–2 hours	0
		2–4 hours	1
		4–6 hours	2
		>6	3
Stage 2	Cervical dilation 5–10 cm	0–2 hours	0
		2–4 hours	1
		4–6 hours	2
		>6 hours	3
Stage 3	Expulsive stage to actual delivery	0–2 hours	0
		2–4 hours	1
		4–6 hours	2
		>6 hours	3
Stage 4	Delivery	Normal attendance	0
		Episiotomy	1
		Low vacuum extraction	2
		High vacuum extraction	3
		Perineal damage to the anal sphincter	2
		Perineal damage through the anal sphincter	3
Stage 5	Postpartum care	Normal attendance	0
		Perineal repair	1
		Retention of the placenta	1

Maximal score 17 Easy labor has a score of zero

A multiple regression model was used to elucidate the main question By comparing the variance explained by the full regression model including variables for main effects and interactions with a reduced model i e the full model minus terms for interaction between the score of the Eysenck Personality Inventory variable and the method of analgesia it was possible to obtain evidence concerning such an interaction

Table II *Mean Subjectively Evaluated Suffering (SES) points in a factorial subdivision and comparison between the inhalation analgesia methods showing significantly lower points ($p<0.05$) after methoxyflurane exposure*

	Nitrous oxide	Methoxy flurane
Labor difficulty ≤ 1	61 4	57 6
No pudendal block	(7)	(21)
Labor difficulty > 1	56 9	50 0
No pudendal block	(21)	(16)
Labor difficulty ≤ 1	63 3	52 8
Pudendal block	(12)	(23)
Labor difficulty > 1	72 7	56 9
Pudendal block	(9)	(24)
Weighted mean	63 5	54 0

RESULTS

An overall comparison of the Subjectively Eva[illegible] Pain Suffering (SES) scores after nitrous ox[illegible] gesia and methoxyflurane nitrous oxide analg[illegible] pectively with the difficulty of labour and pu[illegible] block kept constant showed significantly lowe[illegible] scores after methoxyflurane exposure (Table II) [illegible] indicated lower pain suffering after methox[illegible] nitrous oxide analgesia than after nitrous oxide [illegible] gesia alone

Testing for interaction between Eysenck Perso[illegible] ty Inventory variables and the method of a[illegible] gave the following results

Extroversion *The full regression model* [illegible] significantly more variance than the reduced [illegible] ($p<0.01$) indicating a significant interaction be[illegible] extroversion scores and the type of analgesia [illegible] indicated that the differences between the [illegible] analgesia with respect to SES scores varied [illegible] extroversion scores Table III shows that for [illegible] whose extroversion scores were higher than [illegible] group given nitrous oxide analgesia alone had [illegible] cantly ($p<0.05$) lower SES scores than the gro[illegible] en methoxyflurane nitrous oxide analgesia [illegible] dendal block Table IV shows the comparison [illegible] extroversion scores were 5 or less (introverts) [illegible] group given methoxyflurane nitrous oxide a[illegible] with or without additional pudendal block a[illegible]

ble III *SES points after different types of analgesia Number of observations in parenthesis The only signi ant differences found were for nitrous oxide against methoxyflurane with pudendal block ($p<0\ 05$)*

roversion score>5				
or difficulty	Nitrous oxide	Nitrous oxide and pudendal block	Methoxyflurane	Methoxyflurane and pudendal block
	25 0	62 5	37 5	55 0
	(1)	(6)	(2)	(4)
	50 7	52 5	62 9	76 0
	(7)	(2)	(7)	(5)
ghted means	40 9	56 0	53 2	68 0

wed significantly ($p<0\ 05$) lower SES scores than group given nitrous oxide analgesia with or with pudendal block anaesthesia

Analysis of the effect of the type of analgesia n difficulty of labour and type of inhalation anal ia were kept constant showed that the extrovert turient tended to have a lower but not statistically ificantly different SES score (Table V) when pu dal block was not given This tendency was liable in the introvert parturient group

There were no significant differences in mean SES res between parturients with low and high extro ion scores respectively (Table VI)

iroticism and lie scales The inclusion of neu cism scores and lie scores in the multiple regres i models did not significantly increase the portion explained variance which indicated that these iables did not influence the SES scores particularly l thus could not interact significantly with the hod of analgesia

DISCUSSION

is study was set up primarily to compare the toxi ogical properties of methoxyflurane with those of ous oxide on midwives exposed in alternating three week periods However the experiment could also provide data for an evaluation of the difference in effectiveness between the two gases It would have been preferable to have assigned each parturient indi vidually and randomly to one of the treatment groups Unfortunately such a design is impossible in a toxicologic study on midwives However the draw backs of the three week design were not considered to be of sufficient importance to motivate a separate study of the analgesic effect

In the puerperal ward the parturient was nursed routinely and met the test leader on the second post partum day The test leader did not know the type of analgesia the parturient had received nor did he make any remarks comments or evaluation of his own Thus he ought not to have influenced the results in any systematic manner

The Personality Inventory test by Eysenck and Eysenck (7) has been used in other pain studies (4 12) It is employed routinely at the Psychiatric Clinic in our hospital The visual analogue scale used for Subjectively Evaluated Pain Suffering (SES scores) was strongly recommended by Hayes and Pattersson (10) Freud (9) Aitken (1) Ohnhous and Adler (15) Scott and Kuskinson (16) It has been used in pain as-

ble IV *SES points after different types of analgesia Number of observations in parentheses Methoxyflura with or without pudendal block had significantly lower SES points than nitrous oxide and pudendal block up ($p<0\ 01$)*

tro erts (extroversion score ≤5)				
oor difficulty	Nitrous oxide	Nitrous oxide and pudendal block	Methoxyflurane	Methoxyflurane and pudendal block
	67 5	64 2	59 7	52 4
	(6)	(6)	(19)	(19)
	60 0	78 6	40 0	51 8
	(14)	(7)	(9)	(19)
ighted means	63 8	71 3	50 0	52 0

Table V

	No pudendal block added	Pudendal block added
Extroverts (extroversion >5)		
Nitrous oxide	25 0	62 5
Labor diff ≤1	1	6
Nitrous oxide	50 7	52 5
Labor diff >1	7	2
Methoxyflurane	37 5	55 0
Labor diff ≤1	2	4
Methoxyflurane	62 9	76 0
Labor diff >1	7	5
Weighted means	47 4	63 3
Introverts (extroversion scores ≤5)		
Nitrous oxide	67 5	64 2
Labor ≤1	6	6
Nitrous oxide	60 0	78 6
Labor >1	14	7
Methoxyflurane	59 2	52 4
Labor ≤1	19	19
Methoxyflurane	40 0	51 8
Labor>1	9	19
Weighted means	55 2	59 2

sessment in other studies (3 4) The retrospective assessment of the difficulty of the labor was crude but although it could not grade the severity of difficult labor it separated the uneventful labors from the others

As the Subjectively Evaluated Pain Suffering scores after methoxyflurane analgesia were lower than after nitrous oxide analgesia (Table II difficulty with labor and the use of pudendal block kept constant) one might have concluded that methoxyflurane was a better analgesic in general than nitrous oxide *However subdivision according to the extroversion* variable of the personality inventory test showed otherwise In a smaller group of parturients at the extroversion pole nitrous oxide analgesia gave lower SES scores than methoxyflurane nitrous oxide In the larger group of parturients at the introvert pole of the scale methoxyflurane with or without pudendal block anesthesia gave lower SES scores than the corresponding nitrous oxide analgesia groups Because introverts were more numerous the results in that group dictated the overall results

We could not find any significant relationship between neuroticism and the observed SES scores This seems to be in agreement with findings reported by Eysenck (8) She stated that neuroticism played no part in predicting either behaviour or attitude to labor of the mother Bond and Pearson (4) have shown in women with advanced cervical can[illegible] the presence of symptoms was related t[illegible] neuroticism personality factor whereas the [illegible] dimension of personality was of prime importa[illegible] determining the freedom with which these [illegible] were communicated In the present study we fo[illegible] significant interaction between the extrover[illegible] tor and the type of analgesia Eysenck (8) rep[illegible] that the extroverts rated their pain in labor [illegible] than the introverts and that this reflected a te[illegible] for them to exaggerate the painfulness of the [illegible] tion In this study we could not find any signifi[illegible] difference between low and high extroversion, [illegible] might be due to differences in the registration of [illegible] jectively evaluated pain suffering Eysenck (8) [illegible] verbal registration technique and we used a [illegible] analogue scale technique In a comparative st[illegible] Ohnhaus and Adler (15) the visual analog[illegible] technique proved more reliable than the verbal [illegible] tration technique

In the extrovert group of parturients nitrous [illegible] analgesia gave lower SES scores than meth[illegible] flurane nitrous oxide analgesia In the evaluat[illegible] this difference the tendency of extroverts not to [illegible] approve pudendal block must be considered (T[illegible] VI) We have no explanation for this finding b[illegible] present study indicates that an overall eff[illegible] analgesia can be obtained when choosing betw[illegible] the various methods by taking into account the [illegible] tient s psychological make up

These findings indicate the possible value of [illegible] ther studies on differences in analgesic effects [illegible] respect to personality testing

Table VI

	Introverts ≤5		Extro[illegible]	
Nitrous oxide				
Labor ≤1	67 5	(6)	25	[illegible]
Labor >1	60 0	(14)	50 7	[illegible]
Pudendal block				
Labor ≤1	64 2	(6)	[illegible]	[illegible]
Labor >1	78 6	(7)	52 5	[illegible]
Methoxyflurane in nitrous oxide				
Labor ≤1	59 7	(19)	37.5	[illegible]
Labor >1	40 0	(9)	[illegible]	[illegible]
Pudendal block				
Labor ≤1	52 4	(19)	55 0	[illegible]
Labor >1	51 84	(19)	6 0	[illegible]
Weighted means	56 8		[illegible]	

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APPENDIX

iables for the regression model

0 if standard score for personality inventory parameter was less than or equal to 5 (≤ 5)
1 if higher than 5 (>5)

0 if medically assessed labor difficulty was less than or equal to 1 (≤ 1)
1 if higher than 1 (>1)

0 if the parturient was exposed to nitrous oxide
1 if the parturient was exposed to methoxyflurane

0 if the parturient received a successful pudendal block
1 if the parturient did not receive a pudendal block

$= x_1 \; x$
$= x_1 \; x_3$
$= x_1 \; x_4$ two-way interactions
$= x \; x_3$
$= x_2 \; x_4$
$= x_3 \; x_4$
$= x_1 \; x \; x_3$
$= x_1 \; x \; x_4$ three way interactions
$= x_1 \; x_3 \; x_4$
$= x \; x_3 \; x_4$
$= x_1 \; x_2 \; x_3 \; x_4$ four way interactions

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TREATMENT OF LABOR PAIN WITH LOCALLY APPLIED KETOCAINE

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tract Ketocaine a new local anesthetic drug was used .reatment of referred pain during labor In a randomiz double-blind manner fifty primigravidae received com ses containing either ketocaine in a 10 per cent ethanol tion or compresses with saline (placebo) The com ses were applied to the skin areas where the patient ex nced the most intense pain

ineteen of the 25 patients receiving ketocaine com ses reported good or moderate pain relief for an average 5 h (range 1−5 h) These patients had a mean cervical ation of 3 cm (range 2−5 cm) In patients without ef of the compresses the cervix was dilated to a mean of 6 range 5−8 cm) In patients reporting good effect of the ment pains were located mainly to the back

nly six of the 25 patients receiving placebo compresses .ined relief of pain The effect ceased immediately upon oval of the compresses There was no relation between relief and the degree of cervical dilatation or localiza of the pain

o maternal or fetal side effects related to the treatment registered

candinavian countries narcotic analgesics seda tranquilizers and inhalation analgesics have ned the basis for obstetric analgesia for many s In effective doses these drugs often cause side cts both in the mother and in the child The wide sed blockades may also produce side-effects and ause of possible risks for the fetus paracervical kade has been recommended to be performed on y an experienced obstetrician (4)

pidural blockade provides complete relief of with few side-effects in mother and child How this extensive method may retard labor and if ent oxytocics then have to be used the combina of analgesia and oxytocics was claimed to in ise the risk of fetal distress (8) Furthermore in very early stage of labor an epidural blockade y be more drastic than necessary

.abor pain is considered to be at its maximum at a vical dilatation of 8 to 10 cm but it has been wn that even during the early phase of cervical dilatation some patients especially primigravidae may experience intense pain (3) There is reason to believe that delivery can be delayed in mothers who are stressed because of pain also in the early stage of labor Therefore if during this period an alternative analgesic less dramatic and more safe than those pre viously used was available it would imply an obstet ric advantage

Already in 1929 Rose reported that pain during the first stage of labor referred to the lower abdomen and back could be abolished by infiltration of the skin areas with epicutaneous procaine (7) This fin ding was confirmed by Abrahams 1950 (1)

It was recently shown (5 6) that ketocaine (AB Astra Sweden) a new local anesthetic locally ap- plied on intact skin gives a deep-penetrating local an esthesia The aim of the present investigation was to establish whether pain during labor referred to skin areas above the symphysis and/or sacrum could be decreased or abolished by local application of keto- caine

MATERIAL AND METHODS

Fifty primigravidae were included in the study In a ran domized double blind manner they received compresses containing either ketocaine in 10 per cent ethanol solution or saline (placebo) Each compress was delivered in an air tight envelope of plastic-coated aluminium foil It measured 10 × 14 cm and those with active substance contained 1 g ketocaine (10 ml of a 10 per cent solution)

As can be seen from Table I patients receiving ketocaine were comparable with those receiving placebo with respect to age gestational age and degree of cervical dilatation at the application of the compresses

To an additional 6 patients in whom the absorption of ketocaine was studied compresses containing the drug were applied In these patients blood samples were taken before application of the compresses and at delivery Further more at delivery blood samples from the umbilical cord or the fetus were analyzed for the amount of ketocaine The ketocaine analyses were performed at the research laboratories of Astra AB Södertälje Sweden using a mass-fragmentographic method

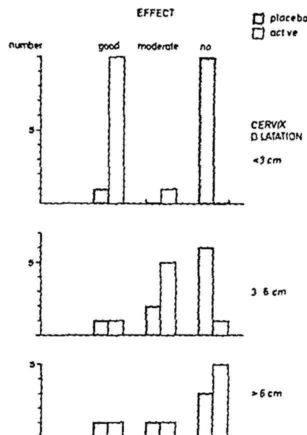


Fig 1 Effect of ketocaine or placebo compresses related to degree of cervical dilatation

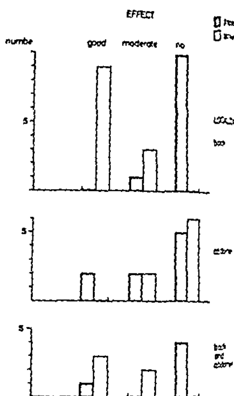


Fig 2 Effect of ketocaine or placebo compresses ... localization of pain

Procedure The investigation was carried out in the delivery ward Before and after application of a compress the cervical dilatation was determined by manual palpation Every patient was observed for one hour

The woman was requested to indicate on the skin where she experienced the most intense pain One or two compresses were applied to this area of the skin If pain was experienced on both abdomen and back compresses were placed at both sites

The compresses were left in position for one hour Then they were removed and the patient s assessment of the effect of treatment was asked for using a simple scale 0 = no effect X = moderate effect and XX = good effect One two and three hours later a new assessment was made Local effects on the skin were registered

No analgesics were given during the time of compress application

The outcome of labor delivery and the condition of the child were recorded in the routine manner used at the department

RESULTS

Of the 25 patients receiving ketocaine compresses 12 reported good effect of the treatment 7 moderate effect and 6 no effect at all (Fig 1) Patients reporting good relief had a mean cervical dilatation of ... (range 2 – 5 cm) at removal of the compresses ... tients reporting no effect the mean cervical dilatation was 6 cm (range 5 – 8 cm) (Fig 1) It was ... that among patients who reported good relief ... 9 out of 12 had their pains localized ... back (Fig 2) The relief of pain lasted on the ... for 2 5 hours (range 1 – 5 hours)

Among the patients receiving placebo ... 3 reported good effect 3 moderate relief ... positive effect at all (Fig 1) In no pat... placebo did the effect of the treatment ... removal of the compresses

In patients receiving placebo the mea... dilatation at removal of compresses was 4 cm ... 2 – 5 cm) (Fig 1) There were no differences ... of cervical dilatation between patients report... and those without relief of pain

No patient complained of side-effects of the ... ment In one woman however a marked ... and edema were found at removal of a ... compress This local reaction persisted for 3 ... had disappeared when the patient left the ... after 7 days

: I *Data on the patients*

	Ketocaine	Placebo
,ears)	22 (19–25)	25 (16–32)
tional age (weeks)	40 (39–42)	40 (39–42)
:al dilatation (cm)	4 (2–8)	4 (1–8)

s

was generally observed that patients receiving :aine more often had erythema and edema of the than patients receiving placebo

) harmful effect on the outcome of labor and ery could be related to the treatment All ren had 1 minute Apgar scores above 8

ıble II gives the maternal and fetal plasma con ations of ketocaine in the 6 patients receiving aine compresses As can be seen the concentra were low both in mother and in fetus In no did the concentration in fetal plasma exceed 25 ent of that found in maternal plasma

DISCUSSION

ırding to previous studies pain during the first of labor is cuased mainly by dilatation of the x and to some degree by uterine contractions (2 he sensory nerves transmitting impulses that pro pain from the uterus enter the spinal cord at through L1 Mild uterine pain as experienced ıg the early part of the first stage of labor is mitted through the middle two (T11 and T12) ıents (2) Pain is also referred to the dermatomes ılied by the corresponding segments i e the r abdominal wall and the skin over the lower ɔal spine and upper sacrum (2 3)

ıe results from the present double blind study v that patients with minor degrees of cervical ation and with pain localized to the back ob- ·d the best relief It seems reasonable to believe at a cervical dilatation >5 cm the patient has ed into a state of a stronger pain Such pain is umably not only referred and therefore not pos to treat by application of local anesthetics This mption is supported by the observation that in 3 ents with moderate effect of the drug cervical dilatation was only 3–4 cm when the compresses were applied but after 2–3 hours the cervix had dilated to 6 and 7 cm These patients reported good relief of pain during the first hour but asked for fur ther analgesics about 1 hour after the removal of the compresses

To evaluate the effect of ketocaine properly all pa tients should have been in a steady state of pain as well as having a constant degree of cervical dilatation during the investigation As such conditions are impossible to obtain under clinical circumstances this must be taken into consideration when evaluating the results

Doubtless patients with a minor degree of cervical dilatation i e less than 4 cm had a good effect of ketocaine compresses compared with those given compresses with saline solution only Furthermore patients with placebo compresses noticed that the re lief of pain disappeared immediately on removal of the compresses In contrast patients with good effect of ketocaine compresses reported that the effect per sisted for about 2 hours after removal

Side effects except for local erythema in some pa tients were not encountered Measurable amounts of ketocaine were found within one hour in the maternal blood and the drug did also pass the placenta How ever the measured concentrations were low and probably without clinical significance

The present results suggest that ketocaine com presses can be used to relieve pain in the early stages of labor To reveal the mechanism behind the pain re lief and to determine the ultimate place of this thera py in clinical practice further evaluations are neces sary

Table II *Concentrations of ketocaine (ng/ml) in sim ultaneous samples of maternal and fetal umbilical arterial and venous plasma Two compresses were ap plied to each patient*

Case	Maternal vein	Fetal umbilical artery	Fetal umbilical vein	Time after removal of compress h
1	61	13	12	3
2	86	15	11	2
3	129	12	31	2
4	93	17	18	4
5	139	30	36	1
6	125	15	17	2

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)RRELATION OF FETAL HEART RATE PATTERNS WITH UMBILICAL ARTERY pH AND CATECHOLAMINES DURING LAST HOUR OF LABOR

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act Fetal heart rate (FHR) patterns were analysed g last hour of labour and correlated to umbilical artery nd catecholamine (CA) levels Fetuses with pathologic IR had significantly higher levels of CA than those with al FHR Particulary high levels were found in fetuses bradycardia and late decelerations
R was further analysed by a computer (DPAC data ssor and computer) in 100 women during last hour of No correlation between deceleration areas or varia and umbilical artery pH and CA was found It is con d that although there is a good correlation between the al FHR pattern and umbilical artery CA and pH it is ssible to quantify the degree of fetal distress by calcula of deceleration areas and variability

ng the last hour of labor pathological fetal rate (FHR) patterns appear in high frequency Non-compromized fetuses were found to have lecelerations in 25 per cent and compromized fe in 50 per cent The predictive value of FHR toring during the second stage of labor has been ioned (5 6 7) To improve the prediction of uterine asphyxia by cardiotocography (CTG) outer analyses of FHR patterns have been intro- d A significant inverse relationship between de ation area and both Apgar score and umbilical as been reported (12) but only partially confirm 3)

e aim of the present study has been to correlate -changes analysed both manually and by a com with umbilical artery catecholamine (CA) levels with pH CA levels in umbilical artery have ear hown to be a sensitive indicator of fetal distress

MATERIAL AND METHODS

tudy was undertaken on two groups of patients moni with cardiotocography (CTG) during the last hour of One group consisted of 89 women 30 of whom had risk pregnancies In this group the FHR patterns were ially evaluated and classified according to Beard *et al* (2) Ninety per cent of the tracing had to be free from acts otherwise that patient was excluded

Another group consisted of 100 women 43 of whom had high risk pregnancies in which the CTG was linked to a computer unit DPAC (data processor and computer Corometrics Los Angeles USA) The principal function of this unit has been described (13) All recordings in both groups were performed with scalp electrodes and intra uterine catheters The following data were processed and printed out by the computer

1 an average base line calculated during 60 heart beats between uterine contractions
2 long term (LT) fluctuations of the FHR i e the sum of amplitude changes in the same direction from beat to beat during a period of 60 heart beats
3 short term (ST) variability being the short fluctuations of FHR expressed as the sum of amplitude changes in different directions from beat to beat during 60 heart beats
4 total variability being the sum of LT and ST
5 early deceleration area calculated 0–40 sec after the start of an uterine contraction defined as a pressure increase of 1 mm Hg/sec for at least 4 sec Both early and variable decelerations would be included in this recording
6 late deceleration area calculated 40–80 sec after the start of an uterine contraction
7 total deceleration area i e the sum of early and late deceleration area

Pudendal anesthesia was given to all women Analgesic drugs were not usually given within 2–3 hours before delivery A great number of artefacts and FHR-changes were observed during vacuum extractions and these cases were excluded from this study Forceps were neither used The umbilical cord was clamped at both ends 15–30 sec after delivery and arterial umbilical blood was aspirated with a syringe The arterial pH was determined with a blood gas analyser (Radiometer BMS Copenhagen Denmark) Plasma was separated and frozen after addition of perchloric acid to a final concentration of 0 4 M Catecholamines were then isolated from the plasma on alumina columns and determined fluorimetrically as described previously (9)

Neonatal depression was defined as a pH below 7 20 and/or an Apgar score at 1 min between 0–6

RESULTS

In the group of 89 women the different types of FHR patterns were correlated to CA levels and to pH values in the umbilical artery (Table I) Fetuses with pathological FHR patterns showed 3–5 fold higher

Table I *Apgar scores umbilical artery catecholamine and pH levels in patients with different types of heart rate patterns*

Fetal heart rate pattern	Apgar 1 /5	Catecholamines (nmol/l)	t test p-value	pH	t test p-value
Normal (n = 17)	8/10	48 8±9 7		7 30±0 01	
Bradycardia (n = 7)	5/9	248 5±130 2	t = 2 43 $p<0\ 05$	7 17±0 03	t = 4 98 $p<0\ 001$
Tachycardia (n = 10)	6/9	205 9±50 9	t = 3 71 $p<0\ 001$	7 18±0 04	t = 3 37 $p<0\ 01$
Variable decelerations (n = 51)	8/10	106 5±12 4	t = 2 38 $p<0\ 05$	7 26±0 01	t = 2 09 $p<0\ 05$
Late decelerations (n = 4)	6/10	243 2±198 2		7 15±0 07	

mean+SEM t test against the normal group

levels of CA and significantly decreased pH compared to those with normal FHR The highest CA levels were seen in fetuses with late decelerations and bradycardia About 85 per cent of the CA were found to be noradrenaline the remainder adrenaline

In Figs 1 and 2 the computer processed data of total variability and late and total deceleration areas were plotted against umbilical artery pH and CA No correlations between these parameters were observed

DISCUSSION

CA are released by the fetus and an increase of the plasma level often seems to precede the development of acidosis (8 9) In fetal lambs CA injected to produce a similar concentration as versus during hypoxia changes the FHR considerably (8) Increased CA levels have been found in human fetuses with pathological FHR (8) and this is confirmed in this study Particularly high levels of CA were seen in the fetuses with base line changes Base line changes have also been observed in sheep fetuses injected with CA in physiological concentrations (1 4) Whether bradycardia or tachycardia will develop depends on the activation of vagal reflexes and to what extent the CA can overcome those The fetuses in our series with variable decelerations had higher CA levels than normal but a slightly but significantly lower pH

This suggests that the occurence of variable decelerations is a sign of fetal distress even if the infants have normal Apgar scores

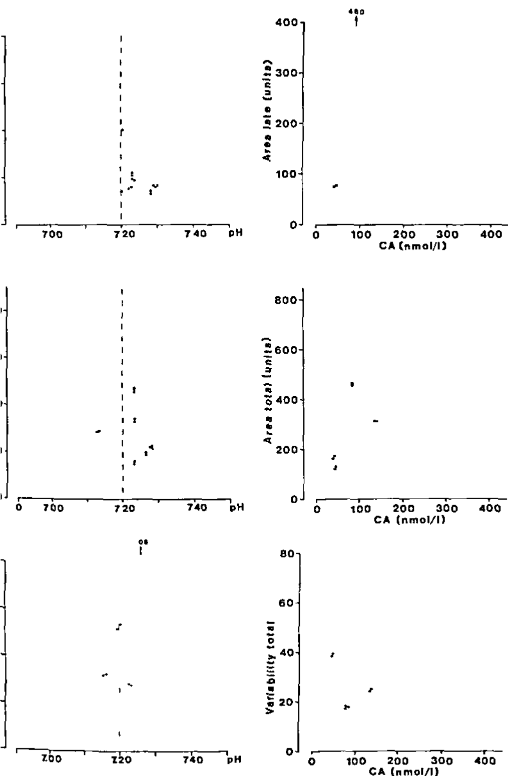
In this study no correlation was observed between computer analysed deceleration areas (late or total) base line or variability during the last hour of labor and Apgar score at 1 min or umbilical artery pH These findings are in contrast to some earlier studies Shelley and Tipton 1971 (12) reported the deceleration area correlated with Apgar score that the mean umbilical pH decreased with mean area However the correlation coefficient calc from their figures of dip area and Apgar score not more than 0 62 Hon s group (13) computer processed data reported a reasonable correlation between various deceleration last hour of labor and Apgar scores at 1 min umbilical artery pH The correlation coefficient however not higher than 0 4 – 0 6 with higher for late deceleration areas Similar results tained in their later report (3) when deceler and fetal scalp pH were compared Co relation ficients between 0 17 – 0 45 were found Wh also included base line levels and variability calculations they found that no single charact of the FHR would be an accurate predictor of scalp blood pH (11)

Even though we found no correlation variability or deceleration areas and pH the with pathological FHR patterns showed sig decreased pH values (Table I) The same is true correlations with CA

In conclusion Increased CA levels pH were observed in all groups with abnormal patterns However it seems to be impossible tify fetal distress from the degree of deceler variability because very subtile changes ca fetal asphyxia

ACKNOWLEDGEMENTS

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Computer processed total variability late and total ...eration areas during last hour of labor plotted against ...lical artery pH

Fig 2 Computer processed total variability late and total deceleration areas during last hour of labor plotted against umbilical artery catecholamine levels

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CONTINUOUS FETAL SCALP TISSUE pH MONITORING DURING LABOR

An analysis of 152 consecutive cases

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ract Continuous scalp tissue pH monitoring was per ied in 152 consecutive cases The success rate was 53 per The average duration of pH monitoring was 151 ites (range 0–609 minutes) A good correlation was d between tissue pH at delivery and blood pH in the ilical artery (r = 0 78) and vein (r = 0 67) In no case normal tissue pH (more than 7 20) and abnormal CTG the Apgar score less than 8 one minute after delivery A ıal tissue pH almost always means that the fetus is not yxiated but a low tissue pH reading may be caused by r factors than acidosis of the fetus Continuous pH itoring during labor remains a research method

iough CardioTocoGraphic Monitoring (CTGM) ıe fetus during labor has been used for the last 15 s (7) there are still doubts concerning the benefit TGM in both high (4) and low (8) risk preg ies Supplementing CTGM with intermittent nation of fetal blood pH reduces the number of etrical operations due to CTGM (4) the disad age of fetal blood sampling (FBS) is however it provides no information about the pH in the rval(s) between the blood samplings

his disadvantage may be overcome if a pH elec le for continuous monitoring is introduced into subcutaneous scalp tissue A miniature pH elec le developed by Stamm *et al* (13) and produced Kontron Roche(R) has been available since 1976 have previously described (18 19) the original pH ıitoring technique and the first results of this ıitoring (in 60 and 50 cases respectively) Further e in a total of 152 consecutive cases (including above mentioned) I have evaluated the value of tinuous pH monitoring in predicting neonatal gar scores (17) The present paper will deal with handling of the pH electrode and the reliability l clinical results of continuous pH monitoring in consecutive cases

MATERIAL AND METHODS

Sixty of the 152 patients were monitored as previously described (19) In the rest of the patients the method was modified Calibration was performed at 37 C (instead of at room temperature) and the the pH was measured by a separate pH meter (PHM73 Radiometer Copenhagen) connected to a cardiotocograph (8030A Hewlett Packard) (formerly Cardiotocograph 540 Kontron Roche was used) The latter modification makes it possible to register pH values between 7 50 and 7 00 on the cardiotocogram whereas formerly only pH values between 7 40 and 7 00 could be registered Furthermore the PHM73 maintains its calibration when the pH electrode is disconnected from the pH meter and during the periods when the power supply to the pH meter is switched off

The pH tracing (Fig 1) is now seen as a dotted line with a pH registration every 10 seconds

The pH tracings are classified as

1 *acceptable* if 1) a constant pH value is obtained shortly after application of the electrode 2) pH does not change more than 0 05 pH units during vaginal examinations including gentle moving of the electrode and 3) pH registration is possible until at least 10 minutes before delivery of the fetal head and
2 *not acceptable* if the above mentioned criteria are not fulfilled

In order to compare the tissue pH value with blood pH a few experiments were made using fetal blood sampling with subsequent pH estimation A good correlation between tissue and blood pH was found (r = 0 90) (19) Furthermore in the acceptable tracings tissue pH taken at the last minute before delivery has been compared to the pH of the blood in the umbilical artery and vein If tissue pH monitoring was not possible during the last 1–10 minutes of labor an ex trapolated value was assumed as extrapolated pH values have been shown to correlate very well with umbilical artery pH (r = 0 83) (17)

In this study the obstetrician looking after the patient did not know the tissue pH and no consequent action was taken

The drift of the electrode was determined after pH monitoring by recalibration in the the buffer solutions of pH 7 00 and 7 40 (37 C) which had also been used for the first calibration Maximal electrode drift was calculated as the difference between the recalibration and the calibration value (if the drift was not the same in both buffer solutions the highest numerical value was used)

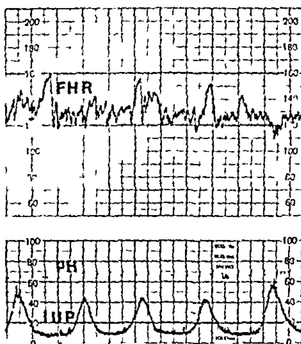


Fig 1 Cardiotocogram with pH registration (dotted line) 0 mmHg equals pH = 7 00 100 mmHg equals pH = 7 50 The pH is stable between 7 32 and 7 34 Paper speed 1 cm/min FHR = fetal heart rate IUP = intrauterine pressure

RESULTS

One hundred and fifty two consecutive pH recordings were made between September 1 1977 and March 1 1979 The majority of women was primiparae (101 = 66 per cent) The pregnancy complications complications during labor neonatal complications and obstetrical operations among the 152 patients are presented in Tables I–IV Some of the

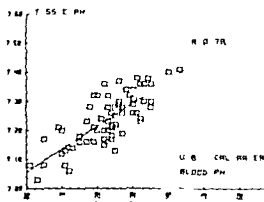


Fig 2 The correlation between the tissue pH at the time of delivery and the umbilical artery blood pH

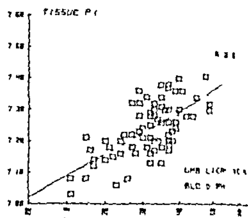


Fig 3 The correlation between the tissue pH at the ti delivery and the umbilical vein blood pH

results of the first 50 and 60 recordings ha b published elsewhere (18 19)

Eighty one out of 152 recordings (53 per cen acceptable Figs 2 and 3 show the correla tween the tissue pH at delivery and pH of the b the umbilical artery and vein respectively Th values of 0 78 and 0 67 both correspond to a p of less than 0 001 There was no change in the relations after modification of the calibra measuring methods (see above)

The drift of the electrode was not correla the duration of pH monitoring (Fig 4) The drift in the 134 cases in which recalibra was formed was less than 0 05 in 73 per cent of th 0 05 – 0 09 in 24 per cent of the cases a dr 0 09 pH units in only 2 per cent of the case not find any change in the drift after chang calibration temperature from room temper 37°C

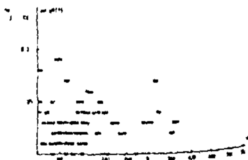
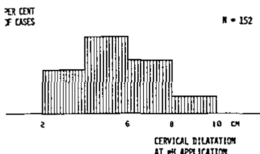


Fig 4 The correlation between the drift of the pH e and the duration of pH monitoring No correla found The correlation coefficient was – 0 002



5 The cervical dilatation at the time of application of H electrode

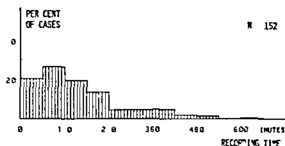


Fig 6 The duration of pH monitoring in the 152 cases

The cervical dilatation at the application of the pH trode appears in Fig 5

The duration of pH monitoring can be seen in Fig The mean duration was 151 minutes (range 0–609 utes)

Two cases of scalp abscesses were observed One of e was treated with incision and antibiotics and other with antibiotics only Both infants were with their mothers at the age of six days

cases of scalp laceration or bleeding needing ring were found

The outcome of the 81 successfully pH monitored veries will be published elsewhere (17) It was nd that the mean tissue pH in neonates with scores of 7 and 8 one minute after delivery was 7 21 (SEM 0 03) and 7 15 (SEM 0 03) respectively whereas the mean tissue pH of children receiving higher Apgar scores was 7 25 (SEM 0 01) Two in fants had Apgar scores of 0–4 one minute after delivery one (case 1) after normal CTGM and a pH higher than 7 20 the other (case 2) had a low pH and an abnormal CTG at the time of delivery

Case 1 Normal pregnancy and labor CTGM with pH monitoring for two hours showed a tissue pH of about 7 30 (7 31 at delivery) and 3 late decelerations 0–4 minutes before spontaneous delivery — otherwise the CTGM was normal The neonate received Apgar scores of 4/10 one/five minutes after delivery The umbilical artery pH was 7 30 The neonatal period was uneventful and the child was discharged from hospital in good condition at the age of six days



7 Cardiotocogram with continuous pH registration l is indicated by the top of the vertical bars)
s tracing was obtained before modification of the meth (see above) Paper speed 1 cm/minute
adycardia and loss of beat to-beat variation is seen at the e time as pH declines from 7 36 to 7 21 in 18 minutes

The pH decline corresponds to a pH decrease of 0 08 units/10 minutes Umbilical artery blood pH was 7 09 The difference between the tissue and the umbilical artery pH (0 12 units) corresponds to a time lag of 15 minutes Apgar scores were 9/10 one/five minutes after delivery

Table I *Pregnancy complications*

	Number		Per cent	
Primipara age ≥30 years	27	(8)	18	(10)
Rhesus immunization	8	(5)	6	(6)
Bleeding before 28th week of gestation	13	(6)	8	(7)
Bleeding after 28th week of gestation	2	(2)	1	(2)
Preeclampsia	8	(5)	5	(6)
Suspected placental insufficiency	6	(5)	4	(6)
Estimated fetal weight ≥3600 g	11	(7)	7	(9)
Postmaturity (≥42th week of gestation)	5	(3)	3	(4)
Other complications[†]	*27*	*(12)*	*18*	*(15)*
No complications	59	(33)	39	(41)

No and per cent in brackets refer to acceptable recordings
[†] One four pregnancy complications as follows IUD in situ epilepsy conization before/during pregnancy obesity arterial hypertension premature labor Caesarean section in earlier pregnancies appendicitis during pregnancy urinary infections during pregnancy stillbirth in earlier pregnancies

Table III *Neonatal complications*

	Number		Per cent	
Perinatal asphyxia[1]	6	(7)	4	(
Apgar score <8 one minute after delivery	18	(6)	1?	(
Apgar score <8 five minutes after delivery	1	(0)	1	
Hyperbilirubinemia[2]	14	(8)	9	(
Weight <2501 g[3]	5	(3)	3	(
Perinatal mortality[4]	1	(1)	1	(
Scalp abscess	2	(0)	1	(
Minor congenital malformations	2	(0)	1	(
Down s syndrome	1	(1)	1	(
No complications	*119*	*(60)*	*7?*	*(*

Number and per cent in brackets refer to
[1] Admitted to the Intensive neonatal department because perinatal asphyxia
[2] One was treated by exchange transfusion the other by therapy
[3] No children were born before the 36th week of gestation
[4] The child died because of cardiac incompensation probably by third trimester intrauterine infection

Case 2 Normal pregnancy except for declining hPL (human placental lactogen) values in the 40th week of gestation leading to induction of labor CTGM with pH monitoring over the last 40 minutes of labor showed a tissue pH of 7 30 until the second stage During the second stage which lasted for ten minutes the pH declined to 7 18 CTGM was normal until two minutes before the second stage began At that time the fetal heart rate decreased from 120 to 60 beats per minute and remained at 60 for the remaining 12 minutes of labor Because of the bradycardia a vacuumextractor was applied during the last five minutes of labor The child showed Apgar scores of 4/10 one/five minutes after delivery The umbilical artery pH was 7 15 The neonatal period was uneventful and the child was discharged in good condition at the age of six days

In Fig 2 it is seen that only one infant had an umbilical artery pH of less than 7 17 when the tissue pH was more than 7 20 This infant had an umbilical artery pH of [illegible] in spite of a tissue pH of 7 21 The recording of [illegible] delivery is shown in Fig 7 A possible explanation of the discrepancy between tissue and umbilical artery [illegible] the tissue pH was 15 minutes behind the [illegible] pH as extrapolation of the pH tracing shows that a pH of 7 09 would have been reached 15 minutes [illegible] delivery The Apgar scores of 9/10 one/five minutes [illegible] delivery correlated however better with the tissue [illegible] with the umbilical artery pH

Fig 2 also illustrates that about 15 per cent of [illegible] table tracings showed a low tissue pH (7 13–7 [illegible]) normal umbilical artery pH (more than 7 20)

Table II *Complications during labor*

	Number		Per cent	
Inefficient uterine action	68	(32)	45	(40)
Suspected fetal distress	37	(17)	24	(21)
Meconium stained amniotic fluid	2	(1)	1	(1)
Cephalopelvic disproportion	8	(2)	5	(2)
Maternal exhaustion	3	(1)	2	(1)
Complication after delivery of the child[†]	11	(7)	7	(9)
No complications	48	(29)	32	(36)

Number and per cent in brackets refer to acceptable recordings
[†] Such as rupture of the uterine cervix placental retention retention of placental cotylodone

Table IV *Obstetrical operations*

	Number		Per cent	
Induction of labor	41	(?6)	[illegible]	
Stimulation of labor	63	(30)	41	
Epidural analgesia	13	(10)	9	
Low forceps delivery/vacuum extraction	36	(15)	[illegible]	
Caesarean section	14	(4)	9	
Operations after delivery[†]	10	( )	7	
No operations	37	(?0)	[illegible]	
No operation (stimulation of labor not included)	63	(35)	41	

Number and per cent in brackets refer to acceptable recordings
[†] Removal of placenta or placental cotylodone manually or ruptured uterine cervix

ble V *Success rate of tissue pH monitoring during or*

erence	Good quality recordings	Number of trials	Per cent
nn & Kelly 1978 (1)	16	31	52[1]
nte *et al* 1978 (2)	44	58	76[1,2]
fei & Saling 1978 (3)	7	22	32[1]
mer *et al* 1978 (5)	35	70	50[3]
mer *et al* 1978 (5)	14	70	20[4]
li 1978 (9)	293	447	66[1,2,6]
rsen *et al* 1979 (10)	30	40	75[1]
tenegger 1978 (11)	29	43	67[1]
bois *et al* 1978 1st (14)	30	55	55[1]
bois *et al* 1978 nd (14)	56	84	67[1]
en *et al* 1978 (15)	47	77	61[1]
et al 1978 (15)	28	77	36[4]
ng *et al* 1978 (21)	43	51	84[1]
et al 1978 (19)	31	50	62[1]
er *et al* 1978 (19)	16	30	32[4]
ent material	81	152	53[5]

umber of u ccessful second stage reco dings not stated/in d

umber of unsucces f l applications not stated

od qual ty rec d ng = successf l eco d g also during the se stage

od qual ty record ng = tissue pH recording in wh ch comparison umb l cal artery pH alue could be pe formed

od quality reco d ng = stable t ss e pH record ng until at least inutes prior to deli ery

umulated dat from 694 trials in 13 centers

DISCUSSION

le I shows the number of good quality recordings he literature in comparison with the present erial Our investigation shows a lower percentage uccessful recordings than most of the other series this is probably due to the following differences ne material

We did not classify our recordings as successful if he fetus was not monitored from application of he pH electrode until 0 – 10 minutes prior to delivery Only in the materials of Henner *et al* (5) and Uzan *et al* (15) was the method of classifica ion similar to ours with approximately the same uccess rate (20 – 50 per cent)

Our recording time was more than 120 minutes in 52 per cent of the recordings (Fig 6) whereas only 29 per cent of the 447 recordings presented by Kubli (9) lasted for more than 120 minutes Although the drift of the electrode is not cor related with the duration of pH monitoring (Fig 4) there is a greater risk of incomplete recordings the longer the duration of pH monitoring (18)

The electrode drift in our material is similar to the drift found in other studies (9) more than 0 04 in 18 per cent of the cases Young *et al* (22) found that the electrode drift was time related our data did not support this (Fig 4) The reason why we did not find the drift to be time related might be that the drift is often most pronounced during the first 15 – 30 minutes of measurement (*in vitro* observation) This means that the duration of calibration is much more important than the duration of monitoring In fact most of our calibrations were performed over long periods as the electrode was often left in the calibration chamber in the morning so only a final calibration was necessary before application of the electrode

The cervical dilatation at the time of application of the electrode was very similar to ours (Fig 5) in the cumulated data presented by Kubli (9) (0 – 4 cm 44 6 per cent 5 – 6 cm 32 8 per cent 7 – 8 cm 15 0 per cent and 9 – 10 cm 7 8 per cent)

Although very few cases of tissue pH monitoring in depressed neonates have been published it seems justifiable to use a tissue pH of 7 20 as the limit between normal and pathological pH for three reasons

1 tissue pH in normal fetuses is very similar to scalp blood pH (20)
2 if Apgar scores decrease from 9 to 8 one minute after delivery the mean tissue pH decreases from 7 25 to 7 21 (see above) and
3 if a tissue pH limit of 7 20 had been used in the management of labor no children would have been born with low Apgar scores because of the tissue pH monitoring (see above)

The very small possibility of a low umbilical artery pH and neonatal Apgar score if tissue pH is normal (see above) justifies our present procedure which does not allow obstetrical operations in cases of pathological CTGM if the tissue pH is normal On the other hand (Fig 2) the relatively high number of false low tissue pH recordings found in the present material and by others (12) does not allow obstetrical operations based only on a low tissue pH

Fig 7 illustrates that there may be a time lag of 15 minutes between the central arterial pH and the tissue pH This is in accordance with the data reported by Hochberg *et al* (6) in the cat Furthermore it illustrates that acidosis for a short period (in this case 15 minutes) does not influence the neonatal outcome as judged by the Apgar score The time lag of 15 minutes should therefore not limit the usefulness of tissue pH monitoring

In another paper (17) I have calculated the sensitivity and specificity of continuous pH monitoring in predicting a neonatal Apgar score one minute after delivery (Apgar score limit between 8 and 9 pH limit between 7 20 and 7 21) I found the sensitivity (67 per cent) and the specificity (73 per cent) of tissue pH monitoring equal to the sensitivity and specificity of cardiotography (50 – 80 per cent and 50 – 90 per cent respectively) and discontinuous pH measurements on fetal scalp blood (50 – 70 per cent and 80 – 90 per cent respectively) found in a survey of the literature (16)

The advantages of continuous pH monitoring are

1 Good quality pH recordings are very easy to interpret With a limit of e g pH = 7 20 everybody can tell when the pH is pathological This is in contrast to the difficult interpretation of a cardiotocogram which may initiate different actions when judged by different obstetricians
2 A number of unnecessary obstetrical operations can be avoided when using continuous pH monitoring (I estimate the number in this series to be 6/81 deliveries (17))
3 The fetus may be asphyctic in some cases with normal CTGM In the paper previously mentioned (17) 2/6 infants with an Apgar score of 0 – 7 one minute after delivery would have been detected by a low tissue pH although the CTGM was normal
4 Only one incision is needed in continuous pH monitoring

The disadvantages of continuous pH monitoring with the present electrode are

1 The high number of cases in which pH monitoring cannot be performed during the second stage of labor As many vacuum extractions and forceps deliveries are caused by ominous CTG patterns a reliable accurate tissue pH recording during the second stage is very important
2 The cases of false low pH readings (see above) mean that obstetrical intervention should not at present be performed because of a low pH reading if it is not followed by a pathological CTGM and/or confirmed by a low capillary blood pH This also means that although the number of obstetrical operations for suspected fetal distress can be reduced by tissue pH monitoring the cases of false low pH readings will have to be eliminated before all fetuses with a normal pH are to escape an operative delivery for suspected fetal distress
3 To prepare the electrode for applica... consuming and the application itself ... specially trained obstetrician/midwife

CONCLUSION

A pH reading of more than 7 2 has al... found to be associated with a high capillary ... bilical artery blood pH (more than 7 15 ex... one case mentioned above) (Fig 2) there... cases of pathological CTGM a tissue pH of m... 7 20 may prevent unnecessary obstetrical ... A tissue pH of less than 7 21 may be a false p... therefore no action can be taken based only ... tissue pH

At present the pH electrode can only be ... research purposes

ACKNOWLEDGEMENT

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CONTROLLED SODIUM BICARBONATE INFUSION AND MATERNAL ACID—BASE BALANCE DURING LABOR

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ract The effects of a controlled sodium bicarbonate) infusion on the acid base balance of primiparas in al labor and delivery were studied and compared to a ar control group of primiparas without S B infusion nning at 6 cm cervical dilatation 2mEq of S B /kg of *body weight were infused to patients in the study until* cervical dilatation The dosage given to this group ged from a study of base deficit dynamics and space ibution of S B in a control group of patients during la and delivery

gnificant variations in pH *base excess and plasma bi* onate were observed beginning 44±19 minutes after B infusion These variations in acid base parameters sted for 10 minutes following delivery

hile no adverse effects were observed in our patients xperimental design represents a preliminary approach rd correcting deleterious fetal acid base variations dur abor and delivery

ing labor and delivery the mother develops a state netabolic acidosis (1) as a result of acute hyper ilation (2) muscular hyperactivity (3) fear and rehention (4) and insufficient peripheral tissue usion (5)

laternal metabolic acidosis contributes to the fetal tive acidosis which is observed during labor and very Any non invasive attempt to influence the l acidosis must be performed via the maternal partment Such studies 6–11 using an arbitrary unt of sodium bicarbonate (S B) failed to ige significantly the fetal acid base balance

MATERIAL AND METHODS

study comprises two groups of primiparas fulfilling the wing conditions uncomplicated singleton pregnancy x presentation without cephalopelvic disproportion ntaneous onset of labor at term no sign of fetal distress nal progress of labor and spontaneous delivery

he first group comprises 12 patients as a control group the second group of 10 constitutes the S B study group Table I indicates the similarity of these two groups Fig 1 il lustrates the partogram of each group while labor was 69 minutes shorter in the S B study group This difference is statistically not significant Both groups were treated iden tically as follows on admission they were infused with *glucose 5 per cent 2 ml per minute During labor only* wet ting of the lips was allowed If membranes were not rup tured on admission amniotomy was performed at cervical dilatation of 4 cm and Pethidine 75 mg Promethazine 25 mg were administered i v All the labors were monitored by *cardiotocography Maternal antecubital vein blood samples* were obtained on admission anaerobically with a hepar inized syringe without venous stasis then at cervical dilation of 4 6 8 cm at full dilation head on pelvic floor and at 10 minutes after delivery Maternal venous blood was used in preference to capillary or arterial blood as it is easy to ob tain It is known that no significant difference in the pH parameters is found between arterial and venous samples (12) The blood samples were analyzed immediately or within 2 hours while kept at 4 C for pH and PCO_2 by blood gas analyzer (Radiometer Copenhagen ABC 1) The Base excess (B E) and plasma bicarbonate were calculated according to the Siggaard Andersen alignment nomogram The hemoglobin value for calculation was 10 gm per cent (Hemoglobin values in all subjects were within the range 9 7 to 11 2 gm per cent)

Table I *Comparison between the study and the con trol group*

	Control group		Study group	
	Mean	SD	Mean	SD
Maternal age (years)	22 3	(3 26)	21 4	(2 50)
Gestational age	39 w	(0 88)	40 w	(1 58)
(weeks days)	273 d	(6 2)	280 d	(11 1)
Pat s admitted with rupt memb (%)	25		20	
Duration of labor (min)	562	(263)	493	(283)
First stage	511	(256)	438	(270)
Fetal weight (g)	3 578	(365)	3 419	(428)
Apgar 1 min	8 75	(1 42)	8 50	(1 96)
Apgar 2 min	9 66	(0 78)	9 30	(1 25)
Apgar 3 min	10 0	(0 00)	10 0	(0 00)

All the d fferences are not statist cally s g ficant

Table II *Acid base balance of maternal venous blood in 12 patients of the control group* [illegible]

Cervical dilation (cms)	Maternal blood 1–2	2–3	4	6	8	F D	P F	[illegible]
pH	7 41 (0 [illegible]5)	7 44 (0 48)	7 46 (0 60)	7 43 (0 34)	7 4 (0 39)	7 41 (0 38)	7.36 (0 4[illegible])	[illegible]
PCO_2 mm Hg	31 6 (6 10)	33 5 (3 40)	[illegible]3 3 (7 0)	31 2 (5 1)	29 6 (6 0)	30 5 (6 3)	28.2 (6 8)	[illegible]
HCO_2 mEq l	19 3 (4 7)	23 7 (5 3)	21 1 (5 5)	20 5 (4 1)	19 7 (4 5)	19 0 (3 [illegible])	15 0 (3 [illegible])	[illegible]
B E mEq/l	4 0 (4 3)	0 1 (5 0)	[illegible]4 (4 8)	2 9 (3 7)	3.2 (4 9)	4 4 ([illegible]4)	8 6 (3 [illegible])	[illegible]

F D = full dilation P F = pelvic floor

In the first group the blood samples were obtained as described and no attempt was made to influence the acid base balance In the second group a solution of 7 5 per cent S B (Abbot Laboratories) was infused according to the following scheme based on the data obtained from the first group In this group it was found that the maximal maternal base deficit occurred when the fetal head reached the pelvic floor (Table I) this value being $-8\ 6 \pm 3\ 5$ mEq/L (mean and SD) We attempted to correct the maternal metabolic acidosis by S B infusion in an amount arrived at by application of the known formula taking into account B E and S B space of distribution (S D) For ease of administration B E was assumed to be -10 mEq/L Furthermore S B space of distribution was estimated at 40 per cent rather than the conventional 50 per cent of total body weight (B W) (13) to minimize the possibility of excessive S B administration The conventional half correction of metabolic acidosis was used to prevent an iatrogenic *metabolic alkalosis (13) Thus the following relationships*

$$\text{S B infused} = \frac{\text{S D} \times \text{B E}}{2} = \frac{\text{B W} \times 0\,4 \times 10}{2}$$

or Amount of S B infused = B W × 2 in mEq of S B

The total amount of S B administered was 2mEq per kg of total body weight The total amount of S B infused varied from 10[illegible] to 176 mEq according to body we[illegible] sions were started at cervical dilation of 6 cm [illegible] until full dilation This timing was chosen because [illegible] decline in maternal pH and the drop in B E [illegible] group I (Figs 2 5) occurred before full cervica[illegible] Considering the time needed for the distribution [illegible] the body and across the placenta the infusion [illegible] started before these changes occurred Conti[illegible] fusion was chosen rather than a bolus adm[illegible] order to prevent an accentuated acute metabol[illegible] and rapid S B excretion in the urine Student [illegible] chosen as the statistical method in this study

RESULTS

The results for the acid base values of the [illegible] group and S B study group are shown in [illegible] *and III Table IV compares the differences* [illegible] PCO_2 plasma bicarbonate and B E in [illegible] blood of the two groups Until cervical d[illegible] cm the differences between the two groups [illegible] mother were not statistically significa[illegible] point on the two groups differ significa[illegible]

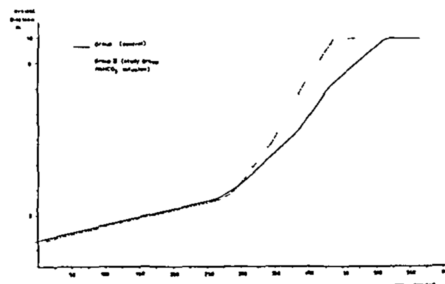


Fig 1 The partogra[illegible] two groups (Mean [illegible]

'le III *Acid base balance of maternal venous blood in 10 patients of the SB study group (mean and S D)*

ncal dilation))	Maternal blood 1–2	2–3	4	6	8	F D	P F	10 min after delivery
	7 36 (0 98)	7 41 (0 21)	7 44 (0 40)	7 43 (0 69)	7 51 (0 42)	7 49 (0 51)	7 47 (0 58)	7 43 (0 48)
')₂ mm Hg	30 2 (8 0)	31 7 (10 4)	27 3 (6 1)	28 3 (7 1)	28 4 (9 0)	29 4 (6 1)	29 4 (7 9)	30.2 (8 8)
)₃ mEq/L	16 0 (0)	19 5 (5 5)	18 4 (3 6)	18 4 (4 3)	2_ 5 (6 3)	23 3 (5 8)	20 9 (5 9)	20 4 (6 3)
mEq/L	8 0 (2.5)	4 0 (5 0)	4 3 (3 1)	4 7 (4 0)	0 2 (5 3)	0 3 (4 8)	1 5 (5 4)	3 0 (6 1)

sodium b carbonate F D = f ll dilation P F = pelvic floor

aternal pH mean and (SD) after S B infusion 7 51 (0 42) at cervical dilation of 8 cm compared 42 (0 39) in the control group ($p<0\ 001$)(Fig 2) larly significant differences in maternal pH oc ·d at full dilation and when the head reached the c floor Ten minutes after delivery maternal pH oth groups was similar (Table I\ Fig 2) and ₂ was not significantly different (Table IV Fig he differences in plasma bicarbonate (Fig 4) and (Fig 5) exhibit similar patterns to those in pH rnal B E was significantly higher in the S B n at full dilation than in the control group being 4 8) versus −4 4 (2 5) mEq/L ($p<0\ 03$ This nce became more pronounced when the head the pelvic floor −1 5 (5 4) compared to −8 6 iEq/L ($p<0\ 003$) No differences in B E per 10 minutes after delivery

Fetal heart rate during labor and the Apgar score of the infants were normal and similar in the two groups No dizziness was noticed in the mother serum sodium and potassium remained stable

DISCUSSION

In the present work two similar groups of primiparas were chosen The amount of S B the time and mode of infusion were based on maternal pH B E and plasma bicarbonate data obtained in a control group Likewise space of distribution and pharmacological dynamics of S B were taken into consideration In this way the pH of the mother rose 0 09 units ($p<0\ 001$) at the stage where cervical dilation was 8 cm This difference was apparent until delivery The

IV *Comparison of acid base balance between the control (Group I) and the study sodium bicarbonate (Group II) (mean and SD)*

ıl dilation		Maternal blood 6	8	F D	P F	10 min after delivery
	I	7 43 (0 43)	7 42 (0 39)	7 41 (0 38)	7 36 (0 40)	7 41 (0.23)
		NS	$p<0\ 001$	$p<0\ 001$	$p<0\ 0001$	NS
	II	7 43 (0 69)	7 51 (0 42)	7 50 (0 51)	7 46 (0 58)	7 44 (0 48)
	I	31 (5 1)	30 (6 0)	30 (6 3)	28 (6 8)	30 (6 0)
₂ mm Hg		NS	NS	NS	NS	NS
	II	28 (7 1)	28 (9 0)	29 (6 1)	29 (7 9)	30 (8 8)
	I	20 (4 1)	20 (4 5)	19 (3 2)	15 (3 5)	19 (4 4)
₃ mEq/l		NS	NS	NS	$p<0\ 02$	NS
	II	18 (4 3)	22 (6 3)	23 (5 8)	21 (5 9)	20 (6.3)
	I	2 9 (3 7)	3 2 (4 9)	4 4 (2 4)	8 6 (3.5)	4 9 (4 3)
mEq/l		NS	NS	$p<0\ 03$	$p<0\ 003$	NS
	II	4 7 (4 0)	0 2 (5 3)	0 3 (4 8)	1 5 (5 4)	3 0 (6 1)

ᵛ, no significance F D = full dilation P F = pelvic floor

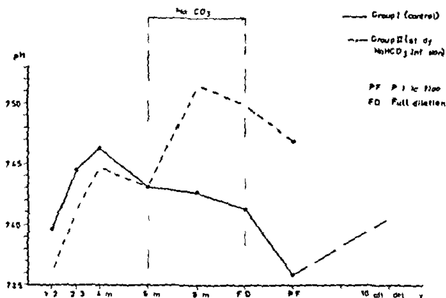


Fig 2 Variation of the maternal pH (mean values) during labor in the two groups

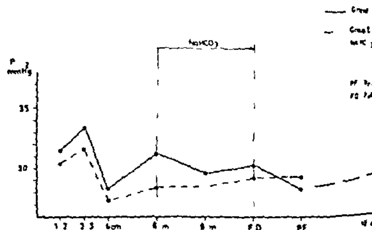


Fig 3 Variation of the maternal PCO_2 (mean values) during labor in the two groups

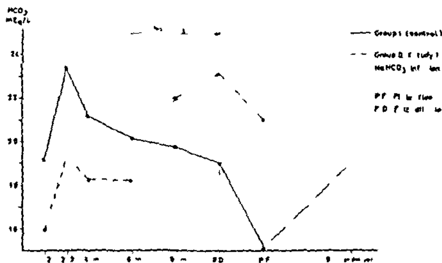


Fig 4 Variation of the maternal plasma HCO_3 (mean values) during labor in the two groups

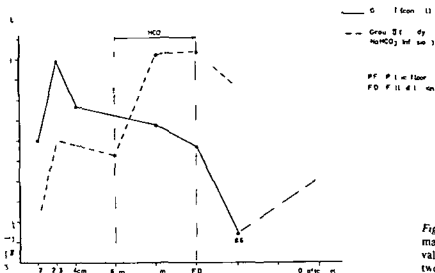


Fig 5 Variation of the maternal Base Excess (mean values) during labor in the two groups

na bicarbonate rose by 6mEq/L ($p<0.02$) only ı the head was on the pelvic floor The B E in ed at cervical dilation of 8 cm but was first ficant at full dilation ($p<0.03$)

e effect of S B administration on maternal pH ne significantly apparent 44 (SD 19) minutes the start of the infusion This time lag probably ıts the distribution time of the SB in the maternal ıartment The time lag was independent of the ınt of S B administered

e effect of S B loading on the mother has to be dered The administration described here ed in a mean maternal pH of 7 51 (SD 0 42) at ıl dilation of 8 cm After this peak pH drop- o 7 44 (SD 0 48) 10 minutes after delivery Thus ısultant metabolic alkalosis is temporary and no ffects which accompany longstanding metabolic osis were observed

e beneficial effect of S B on the fetus was found ımal studies A prolonged survival time was ıed in asphyxiated fetal lambs when bicar te and glucose were given (14) In asphyxiated ey fetuses treated with bicarbonate and glucose ıcidence and magnitude of brain stem damage reduced (15) In both these animal studies the s were similar but less pronounced when S B he sole medication

ıese observations justify further studies in ıns in order to reduce fetal acidosis in labor and ıery It seems probable that during fetal asphyxia the rate of production of acid metabolites is relatively small compared to maternal buffer stores It would therefore seem logical that in planning such studies the results obtained from the present work in the mother could be taken into consideration as a starting point

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TRANSVAGINAL FETOSCOPY IN ANTERIOR PLACENTAS

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stract When the placenta is located anteriorly fetoscopy he abdominal route may be impracticable An alterna route i e insertion of the fetoscope through the anteri aginal fornix was used in 31 women in midpregnancy nty six of the women had been admitted for therapeutic tion the remaining five for diagnosis The insertion of nstrument was uncomplicated in all 31 women In three ie five diagnostic cases the disease at risk was excluded three women continued their pregnancies and two of i went on to term without complications The third ıan had intermittent leakage of amniotic fluid At 33 s she was delivered of a normal infant (birthweight) g) Transvaginal fetoscopy may be considered when nterior placenta has an extension so broad that the abinal approach is unfeasible

n a placenta covers the entire anterior wall of the us a fetoscope inserted by the abdominal route damage the placenta with death of the fetus as a lt (1 10) But such a complication can be avoided nsertion of the instrument through the anterior nal fornix We report here our experience with method

PATIENTS AND METHODS

y-one women were selected for this study They were in 6th to 24th week of gestation Ultrasound examination hown the placenta to be located anteriorly Twenty-six e women were admitted for therapeutic abortion the ining five for diagnosis

ith the woman in the lithotomy position the bladder mptied by catheterization The vulva and vagina were d with an antiseptic solution The area where the portio es with the anterior vaginal fornix was disinfected with ie and anesthetized With the cervix held in position a tenaculum a sharp trocar and cannula 2 2 × 2 7 in outer diameter were inserted parallel to the cervix in e amniotic cavity The trocar was removed and an en ope 1 7 mm in outer diameter (Needlescope Dyo- Woburn Massachusetts) was inserted through the ula (A 150 mm long endoscope was used in the first cases (5) *thereafter a 170 mm long instrument*) A uge needle was advanced through the channel gside the endoscope Under direct visual control placen essels were punctured without any attempts at cannulation and the stream of blood that issued into the amniotic fluid was aspirated Usually two or three vessels were punctur in each case

The proportion between fetal and maternal red cells was determined by the Kleihauer staining for HbF in each sample (8)

Anti D gammaglobulin was given to rhesus negative women To prevent uterine contractions a beta receptor stimulator terbutaline (Bricanyl Astra Pharmaceuticals) was infused during fetoscopy In continuing pregnancies terbutaline per os was then prescribed until the end of the 36th week of gestation

RESULTS

The insertion of the fetoscope was uncomplicated in the 26 women in the methodology study There were no signs of damage to the urinary bladder thus in all women the urine was invariably clear In one woman who was in the 24th week of gestation the instrument (150 mm long) was too short to reach the placenta In the remaining 25 women placental vessels were punc tured In one of these women the samples contained only maternal red cells In three of the women 60 85 and 85 per cent of the cells were of fetal origin in the sample that had the highest percentage of fetal red cells In the remaining 21 the corresponding figure was > 95 per cent

Diagnostic cases Out of five women admitted for prenatal diagnosis the fetus in two was found to have the disease at risk and pregnancy was terminated In the remaining three who thus had unaffected fetuses two pregnancies went on to term without complica tions one woman was delivered at 38 weeks the other at 40 weeks The third woman that had an unaffected fetus had undergone amniocentesis twice before fetoscopy 6 and 3 weeks previously In this woman the fetoscopy was followed by intermittent

Two fetuses wer at risk for hemophil A one for hemophilia B (6) and o e f on Willebrand s disease (7) in the fifth case fetoscopy was done for chromosomal stud es (3)

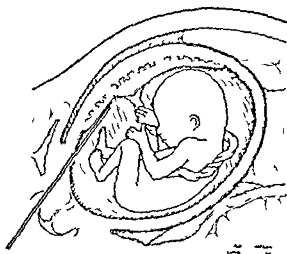


Fig 1 The fetoscope inserted by the transvaginal route

leakage of amniotic fluid to the vagina Labor started in the 33rd week She was delivered of a 2 15 kg normal girl with a 1 minute Apgar score of 9 and a 5 minute score of 10

No signs of infection were observed in the three women who continued the pregnancy

DISCUSSION

According to Elias (4) one of the largest series of fetoscopy all done by the *abdominal approach* is that of Hobbins and Mahoney at Yale University In that series 79 pregnancies were allowed to continue after fetoscopy Five of them ended in spontaneous abortion in three cases due to amnionitis in one case to umbilical cord laceration and in one to placental abruption Seven pregnancies ended in premature delivery Of the infants thus far delivered none has shown any deleterious effects as a result of the procedure There has been no maternal morbidity

In the present study no early complications of fetoscopy by the *transvaginal route* were seen in any of the 31 women examined But the number of continuing pregnancies was too small to admit any conclusions about the risk of abortion or premature delivery with this method We feel that until further experience with transvaginal fetoscopy has been gained the abdominal approach with its well-documented low frequency of abortion and premature delivery is the method of choice in those cases of anterior placenta where the instrument can be i[illegible] to the placental margin (2 9 11) But [illegible] anterior placenta has an extension so broad [illegible] abdominal entry is unfeasible the transvag[illegible] may be considered Technically the inser[illegible] instrument through the anterior vaginal [illegible] easy since there is no abdominal wall to [illegible]

ACKNOWLEDGEMENT

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DIAGNOSTIC ULTRASOUND IN THREATENED ABORTION AND SUSPECTED ECTOPIC PREGNANCY

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ict 200 women threatened with abortion during the 6 weeks of pregnancy were examined with diagnostic ound to determine whether there were signs of intra e life Of the 90 who showed positive signs 8 aborted ineously later the other 82 continued their pregnancy ultrasound investigation revealed no signs of intra e life in 110 patients Of these spontaneous abortion r evacuation because of missed abortion 101 (histo ogical examination showed degenerated villi in 98) egnant 4 mola hydatidosa 3 extrauterine pregnancies

ultrasound examination was performed to ascertain er 136 women with suspected ectopic pregnancy had terine pregnancies 61 of them had an intrauterine ional sac confirmed at clinical follow up One of the s operated on with laparoscopy because of pain no malities were found In 36 of the other 75 laparos was performed Ectopic pregnancy 21 ovarian or par in cyst 11 adhesions 2 salpingitis 1 and normal 1 gnostic ultrasound is excellent for accurate prognosis eatened abortion Unnecessary operations avoided alization in suspected ectopic pregnancies reduced

itigation with ultrasound early in pregnancy has possible only for the past decade The value of investigations depends on the certainty with h an intrauterine gestational sac can be seen and her signs of intrauterine life can be positively onstrated Most investigations have demonstrat tal heart action from week 7 to 8 of pregnancy have shown that a living fetus is a good prognosis ontinued pregnancy (1 – 11) The fetal heart ac can be seen on the monitor of a real time scanner n the A scan of a compound scanner

early pregnancy the gestational sac could be as a clearly outlined echo-free space in the uterus ie ultrasound equipment monitor (12) In week 5 regnancy the diameter of the echo-free space is 1 and the growth is very rapid

very experienced gynecologist is familiar with atened abortion symptoms and the highly fascet clinical picture of ectopic pregnancy Therefore do not further discuss this here

PATIENTS AND METHODS

To evaluate the diagnostic ultrasound in threatened abortion and suspected ectopic pregnancy we investigated for 18 months all pregnancies with these two disorders at the Department of Obstetrics and Gynecology in Lund The investigations were made either on a real time scanner (Vidoson Siemens) or on a compound scanner (Diasonograph Nuclear Enterprise)

In 200 women with abortion threatened during the first 16 weeks of pregnancy we looked for fetal heart action or fetal movements from week 9 of pregnancy From week 5 to 8 we measured the diameter of the intrauterine gestational sac according to Hellman *et al* (12) and determined its growth in two investigations with an interval of at least one week

In 136 women with suspected ectopic pregnancy we looked for an intrauterine gestational sac

RESULTS

Of the 200 women with threatened abortion 90 had *signs of intrauterine life 8 of the 90 aborted sponta* neous later the other 82 continued their pregnancy

The ultrasound investigation revealed no signs of intrauterine life in 110 women 101 of them aborted spontaneously or were evacuated later because of missed abortion (histopathological examination showed degenerated villi in 98) 4 were not pregnant 3 had mola hydatidosa and 2 had ectopic pregnancy (Table I)

Table I *Result of ultrasound investigation compared with the outcome of pregnancy*

	Result of ultrasound investigation	
Outcome of pregnancy	Life signs	No life signs
Pregnancy continued	82	0
Ectopic pregnancy	0	2
Mola hydatidosa	0	3
Spontaneous abortion	8	101
No pregnancy	0	4
Total	90	110

Table II *Result of ultrasound investigations in suspected ectopic pregnancies*

Outcome of pregnancy	Result of ultrasound investigation	
	Intrauterine gestational sac	No intrauterine gestational sac
Pregnancy continued	44	1
Therapeutic abortion	9	0
Spontaneous abortion	8	13
No pregnancy	0	40
Ectopic pregnancy	0	21
Total	61	75

Of 136 patients with suspected ectopic pregnancy 61 had an intrauterine gestational sac 44 of the 61 women continued the pregnancy 9 had a therapeutic abortion and 8 aborted spontaneously None of the 61 had an ectopic pregnancy

No intrauterine gestational sac could be seen in 75 of the 136 patients

In fact one of them had an intrauterine pregnancy in week 4 of pregnancy one week later an intrauterine gestational sac could be seen 13 were diagnosed as spontaneous abortions before the ultrasound investigation was performed 40 women were not pregnant 21 had ectopic pregnancy (Table II)

Laparoscopy was performed in 36 of the 75 patients without a visible intrauterine gestational sac on ultrasound (Table III) 21 of them had ectopic pregnancy 11 had ovarian or parovarian cyst 2 had adhesions 1 had salpingitis and 1 was normal

One of the 61 women who had a demonstrable intrauterine gestational sac on ultrasound was operated on with laparoscopy for abdominal pains and a normal intrauterine pregnancy was seen

Of the 21 patients with ectopic pregnancy 16 had positive pregnancy test (HCG in urine) whereas 5 had negative tests As a comparison 11 of the 13 women with spontaneous abortion had positive pregnancy test

DISCUSSION

Women with threatened abortion where no signs of intrauterine life can be noted in one or two ultrasound investigations do not have a living fetus With modern ultrasound apparatus there is no difficulty in finding an intrauterine pregnancy from the 5–6th week of pregnancy and from the 7–8th week in detecting fetal heartbeats If signs of life can be demonstrated the prognosis is very good and the [illegible] cy has a 90 per cent chance to continu [illegible] abortion ultrasound investigation gives a [illegible] safe prognosis and if there is an intra [illegible] nancy without signs of heart activity the [illegible] be evacuated thereby avoiding unnecessary [illegible] and pain and reducing the need for hos[illegible]

Diagnostic ultrasound in cases of su[illegible] nancy is most valuable in those patients [illegible] trauterine gestational sac can be demons[illegible] was possible in 61 of 136 in our material

In 60 of the 61 patients unnecessary [illegible] were avoided all 60 could leave the hosp[illegible] hours after the ultrasound investigation

In cases of threatened abortion and su[illegible] topic pregnancy measurements of HCG [illegible] normally useless Only when ultrasou[illegible] demonstrate any intrauterine gestatio[illegible] when there is no vaginal bleeding could a [illegible] pregnancy test be of value and indicate [illegible] nancy In several cases recently we have [illegible] the ectopic pregnancy together with an [illegible] with ultrasound Modern real time appara[illegible] the diagnosis more certain and all inves[illegible] made with a full urine bladder whereby [illegible] an excellent picture of the entire uterus The[illegible] been any false positive results we have [illegible] where the sometimes thick and partly [illegible] dometrium or decidua has been mistaken [illegible] pregnancy or an abortion in progress If the [illegible] are primarily uncertain the investiga[illegible] repeated in about one week

Even if the ultrasound demonstration of [illegible] tional sac does not exclude the possibility of [illegible] topic pregnancy with both intra and [illegible]

Table III *Result of ultrasound investig[illegible] pared with result of laparoscopy in suspecte[illegible] pregnancies*

Result of laparoscopy	Result of ultrasound [illegible]	
	Intrauterine gestational sac	No [illegible]
Ectopic pregnancy	0	21
Ovarian parovarian cyst	0	11
Adhesions	0	
Salpingitis	0	1
Normal	1	1
Total	1	35

uses the possibility of an ectopic pregnancy is very all definite symptoms must be present to justify operation An empty uterus can indicate that the is not pregnant that the pregnancy is so early it it cannot yet be detected by ultrasound that the ient has already aborted or that she has an ectopic gnancy As mentioned above an ultrasound in tigation in one of our patients was negative in the week of pregnancy but one week later an intra ne amniotic sac could be seen If no intrauterine ional sac can be demonstrated the clinical pic will decide whether operation is necessary asurement of human chorionic gonadotrophin in e can be useful in these situations

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CONTRACEPTIVE HABITS IN WOMEN BETWEEN THIRTY AND FIFTY YEARS OF AGE

A comparison of two periods 1967–69 and 1972–74

E Bostofte and O Berg

From the general practitioners of the southern part of Storstrøms County and the Patho-anatomical Department and the Department of Obstetrics and Gynecology Central Hospital Nykøbing F Denmark

ract The use of contraception by women 30–50 years ge is presented The material was composed of par in the prophylactic investigations for cancer colli in the southern part of Storstrøms County which was performed in the period 1967–69 and secondly in –74 A total of 17 078 women were examined of om 8 234 participated in both surveys A comparison of two periods of investigation revealed a significant in ase ($p<0.01$) in the utilization of contraception and in fting to more effective methods This improvement was ibuted to the increased amount of information about traceptive methods which was made available in the ntry It was observed that a remarkably large percentage the women did not use contraception 24 9 per cent ong those 30–34 years of age 26 9 per cent among those 39 years of age 40 7 per cent among those 40–44 years ge and 57 2 per cent among those 45–49 years of age lysis of the influence of socioeconomic conditions wed that women of the lowest social stratum with slight cation and low income made up a large proportion of se who abstained from contraception The number of gnancies was found to play a role in the use of contracep- An expansion of the distribution of information about traception to the public is recommended as well as a sible economic subsidy to the socially disadvantaged for curement of contraceptives

ecent years considerable progress has been made he development of methods of contraception At we have so many different types of effective traceptives such as combination preparations se nce preparations progesterone acting prepara s both in tablets and for injection various types UD diaphragms and condoms that anyone is in osition to employ at least one suitable method and ain satisfactory protection

t the same time dispensation of information ut contraception has improved remarkably and n made easily comprehensible The mass media in ious ways has discussed the concept of contracep- Schools almost everywhere have given instruc t in sexuality and guidance in contraception Con eption clinics are available all over the country and brochures about contraception are dispensed without charge from hospitals doctors midwives etc

Consequently it should be possible for everyone both men and women to become acquainted with the existing types of contraceptives and to secure ade quate protection assuming that pregnancy is not desired

The main purpose of this work has been to ascer tain the contraceptive habits in a section of the popu lation and to detect any changes in these habits after an eight year interval in order to evaluate the influ ence that the improved development of and infor mation about effective methods of contraception has had on the use of contraception

A second objective was to determine whether so- cioeconomic circumstances and the number of preg nancies influence the utilization of contraception

MATERIAL AND METHODS

The material was composed of participants in the two pro- phylactic investigations of cancer colli uteri in women 30–50 years of age carried out in the southern part of Storstrøms county (previously Maribo county)

The first investigation was performed in the period 1/9 1967 to 1/8 1970 (1) and the second in the period 1/10 1971 to 15/7 1975

Table I shows the patient material In 1967–69 15 359 women 30–50 years of age were invited to participate in the investigation of whom 13 255 (86 3 per cent) accepted In 1972–74 14 408 women in the same age group were asked to participate and 12 007 (83 3 per cent) accepted

Table I *Patient material*

	1967–1969		1972–1974	
	No	per cent	No	per cent
Examined	13 255	86 3	12 007	83 3
Not examined	2 104	13 7	2 401	16 7
Total	15 359	100 0	14 408	100 0

Table II *Distribution of different contraceptive methods expressed in percentages in five-year [illegible] Material 1967 – 1969*

Contraceptive methods	30 – 34	35 – 39	40 – 44	45 – 49	Total material per cent	Total material No
No	3 0[illegible]0	3 3[illegible]8	3 [illegible]97	3 310		13 [illegible]
No contraception	[illegible]8 7	34 9	46 1	63 9	43 7	5 [illegible]
Withdrawal	9 8	13 1	13 2	12 0	12 1	1 6[illegible]
Other methods	1 8	2 5	2 1	1 6	2 0	2[illegible]
Condom	26 8	25 3	22 9	13 9	[illegible] 1	[illegible] 9[illegible]
Diaphragm	7 5	6 1	4 4	2 1	4 9	6[illegible]
Hormonal contraception	[illegible]1 1	14 5	7 3	3 1	11[illegible]	1 4[illegible]
IUD	1 7	0 6	0 4	0 1	0 6	86
Sterilized	2 6	3 0	3 7	3 4	3 2	4[illegible]
Total	100 0	100 0	100 1	100 1	99 8	

The primary investigation was performed by the 60 general practitioners of the county who in addition to obtaining tissue samples carried out an objective examination of the genitalia rectum and breasts as well as a relatively detailed gynecological-obstetric anamnesis including questions about contraception utilization ([illegible] 3 4)

There were a total of 25 262 examinations which included 8 234 women who participated in both surveys

The data collected were programmed into EDP and have formed the basis of this investigation

Statistical analysis was carried out by the χ^2 test at a significance level of 1 per cent Only p-values below that level are mentioned Most of the differences in this work were highly significant with a value of 0 1 per cent The significant differences in the tables are designated by arrows

When sterilization is specified for women it indicates all types of gynecological intervention that brought about permanent sterility These include hysterectomy salpingectomy etc

The copper spiral was available for only a short while towards the end of this investigation namely from 1/1 1974

The expression other methods [illegible] rhythm vaginal douche and foam Classification [illegible] economic groups was carried out according to [illegible] and Wolf (1[illegible])

RESULTS

Tables II and III shows the frequency [illegible] various methods of contraception were [illegible] frequency of failure to use contraception [illegible] by age groups composed of five-year [illegible]

It is immediately evident by comparison [illegible] totals that there was a significant decrease [illegible] failure to use contraception from 19[illegible] [illegible] 1972 – 74 This decrease was accompanied by [illegible] lar significant decline in the employment of [illegible] drawal other methods and of the condom [illegible]

Table III *Distribution of different contraceptive methods expressed in percentages in five-year [illegible] Material 1972 – 1974*

Contraceptive methods	30 – 34	35 – 39	40 – 44	45 – 49	Total material per cent	Total material No
No	[illegible] 969	[illegible] 9[illegible]	2 934	3 118		1 [illegible]
No contraception	4 9 ↓	6 9 ↓	40 7 ↓	[illegible]7 2 ↓	↓ 37 6	4 [illegible]
Withdrawal	2 6 ↓	6 1 ↓	4 2 ↓	4 0 ↓	↓ 4 2	[illegible]
Other methods	0 8 ↓	0 4 ↓	0 4 ↓	0 5 ↓	↓ 0 [illegible]	64
Condom	[illegible]3 0 ↓	23 3	18 4 ↓	12 5	↓ 19 [illegible]	[illegible]
Diaphragm	6 5	6 1	4 0	2 4	4 7	[illegible]
Hormonal contraception	33 1 ↑	[illegible]6 2 ↑	15 8 ↑	[illegible] 1 ↑	↑ 20 4	[illegible]
IUD	5 4 ↑	2 8 ↑	1 7 ↑	0 2	↑ [illegible] 5	[illegible]
Sterilized	3 7	8 [illegible] ↑	14 8 ↑	16 1 ↑	↑ 10 8	1 [illegible]
Total	100 0	100 0	100 0	100 0	99 9	

↓ = Significant fall compared with 196[illegible] – 1969

↑ Significant increase compared with 196[illegible] – 1969

le IV *Distribution of contraceptive methods expressed in percentages in different socio-economic groups erial 1967–1969 Age 30–39 years*

	Socio-economic groups					Total material	
ˡraceptive methods	4	5	6	7	8	per cent	No
	205	602	1 696	2 107	1 725		6 335
ontraception	25 9	28 1	28 1	30 5 →	39 7	31 7	2 0'4
idrawal	2 4	6 5 →	12 2	12 3	12 8	11 5	731
r methods	5 4	3 0	2.3	1 9	1 5	2 1	136
dom	24 9	28 1	27 4	27 0 ←	22 7	26 7	1 645
hragm	16 1	12 1 ←	7 8	7 0 ←	2 6	6 8	4.9
nonal contraception	23 9	19 6	19 0	18 3 ←	14 2	17 7	1 119
	1 0	2.2	1 4	0 9	0 6	1 1	70
lized	0 5	0 5	1 8	2 1 →	6 0	2 9	181
l	100 1	100 1	100 0	100 0	100 1	100 0	

gnificant increase between the groups
gnificant fall between the gro ps

y the significantly increased use of all contra : methods was due to an increase in the most ef methods i e hormonal contraception IUD :rilization Use of the diaphragm was unchang

ection of the individual age groups shows in nvestigations that failure to use contraception ignificantly with increasing age though not he 30–34 to the 35–39 year group in the se survey In addition the same tendency to a : in the use of withdrawal other methods e condom and of an increase in the use of hor contraception IUD and sterilization can be in the individual groups as well as in the total t material There are however some excep- Condom utilization was unchanged in the) and in the 45–49 year groups sterilization was unchanged in the youngest age group and utiliza tion of IUD was unchanged in the oldest age group use of the diaphragm was unchanged in all age groups

Table IV V VI and VII show the methods of con traception in relation to the classification of the material according to socioeconomic groups For the sake of clarity the material has been divided into 10-year age groups 30–39 and 40–49 years since no additional information was obtained by arranging the groups in five year intervals

Comparison of the tables shows that almost the same tendency existed in all the groups in the use or failure to use contraception In general there was the same signficant decrease and increase apart from a few exceptions With a decline in the level of social status there was a clear indication of the utilization of

V *Distribution of contraceptive methods expressed in percentages in different socio-economic groups ial 1967–1969 Age 40–49 years*

	Socio-economi groups					Total material	
iceptive methods	4	5	6	7	8	per cent	No
	24.	602	2 042	1 901	2 096		6 89.
ntraception	43 8	50 9	51 4	55 2 ←	59 4	54 6	3 761
rawal	6 6	10 1	13 0	1 0	14 3	1 6	871
methods	8 7 ←	2 5	1 7	1 6	1 3	1 9	1.9
om	'0 7	19 6	21 3	.0 3 ←	13 8	18 6	1 .'9
ragm	8 7	7 5 ←	3 8	2 8 ←	1 4	3.3	.27
onal contraception	8 7	5 9	6 6	5 3 ←	3 3	5 3	36
	0 2	0 8	0 2	0 1	0 1	0.	16
zed	2 7	2 6	.0	.8 →	6 3	3 6	.47
	100 1	99 9	100 0	100 1	99 9	100 1	

gn fca t ncrease between th groups
gn ficant fall between the groups

Table VI *Distribution of contraceptive methods expressed in percentages in different socio-eco…*
Material 1972 – 1974 Age 30 – 39 years

	Socio-economic groups					Total material	
Contraceptive methods	4	5	6	7	8	per cent	No
No	163	749	1 676	2 030	1 335		5 953
No contra eption	17 1	21 9	23 4	24 9 –	33 9	25 9	1 543
Withdrawal	1 2	2 0 –	4 4	4 9	5 2	4 3	[illegible]
Other methods	1 2	1 1	0 6	0 5	0 4	0 6	36
Condom	15 3	20 4	24 3	26 2 –	19 4	23 1	1 3 6
Diaphragm	17 2	12 8 –	6 6	5 4 –	2 5	6 3	3 6
Hormonal contraception	34 4	33 0	31 2	30 3 –	24 3	29 6	1 6[illegible]
IUD	9 8	6 3	5 0 –	3 1	2 7	4 1	44
Sterilized	3 7	2 5	4 5	4 9 –	11 6	6 0	355
Total	99 9	100 0	100 0	100 2	100 0	99 9	

– S gnifi ant in rease between the groups
– S gnifi ant fall between the groups

less effective or no contraception Highly significant differences in the tables are designated by arrows A pronounced rise in the number of sterilizations can be seen in the lowest socioeconomic group which was not wholly unexpected

Table VIII lists the utilization of contraception with regard to the number of pregnancies This table combines all contraceptive methods (excluding no contraception) since differentiation according to individual methods exhibits interesting relationships only with respect to sterilization The same inclination was observed in all age groups in both investigations namely that a large percentage of the women who had never been pregnant abstained from contraception However contraception utilization rose steeply after the first and second pregnancies and became stable only after the third pregnancy

Table IX records the number of surgica… women in relation to the number of pregna… can be seen that a relatively large percen… women who had never been pregnant were… A correspondingly high sterilization is se… women who had given birth 4 times T… of sterilization among women with 5 … cies was not surprizingly quite high a… cent among the 40 – 49 year group in 197…

DISCUSSION AND CONCLUSIONS

Our results signify a significant increase in the … tion of contraception during the investigat… 1967 – 75 and show that the increase was ex… ively to the employment of safer methods …

Table VII *Distribution of contraceptive methods expressed in percentages in different socio-econo…*
Material 1972 – 1974 Age 40 – 49 years

	Socio-economic groups					Total material	
Contraceptive methods	4	5	6	7	8	per cent	No
No	210	475	1 794	1 876	1 749		6 054
No contraception	34 3 –	51 2	45 7	47 4 –	55 9	49 2	[illegible]976
Withdrawal	1 9	2 5	4 5	4 7	3 7	4 1	[illegible]
Other methods	2 9 –	0 0	0 8	0 2	0 3	0 5	[illegible]
Condom	15 2	12 6 –	17 8	17 4 –	11 6	15 4	93
Diaphragm	9 5	4 4	4 5 –	2 6 –	1 3	3 2	19
Hormonal contraception	13 8	16 2	11 8	12 3 –	8 2	11 3	685
IUD	4 8	1 3	1 0	0 9	0 3	0 9	56
Sterilized	17 6	11 8	13 9	14 7 –	18 7	15 5	913
Total	100 0	100 0	100 0	100 2	100 0	100 1	

– = Significant increase between the groups
– = Significant fall between the groups

VIII *Total use of contraception expressed in percentages in relation to the number of pregnancies ...al 1967–1969 and 1972–1974 Age 30–50 years*

...oups	No of pregnancies 0	1	2	3	4	5	Total no
1969							
39 years	16 5 –	47 4 –	75 4	78 3	80 2	76 6	6 348
49 years	9 2 –	31 0 –	49 7	53 6	52 6	54 7	6 907
1974							
39 years	22 7 –	56 9 –	78 7 –	84 2	81 9	83 8	5 953
49 years	22 8 –	37 9 –	49 7 –	55 6	59 1	63.3	6 054

...nificant increase between the number of pregnancies

...onal contraception IUD and sterilization ... results are in complete agreement with other ...s (5 6 16)

...ertheless it is surprizing that such a large per...ge of women still failed to use contraception ...e the encouraging increase in its utilization ... among the women aged 30–39 years there were ...r cent who abstained from contraception It is ...possible that the true percentage is still larger ... this survey was concerned only with women ...participated in the cancer prophylactic investiga... The women who did not attend constitute 14 ...ent and 17 per cent respectively and from other ...s it has been established that the non attending ... represents a high risk segment of the popu...n with regard to cervical cancer (10 13) More ... that group consists predominantly of women ... the lower socioeconomic stratum Consequent... is quite probable that that group utilizes less ef...e types of contraception or none at all

... acquaintance with the Danish statutes on abor...and sterilization is considered to be an important ...r in an assessment of the results of this work ...ng the period of this investigation there occurred a considerable liberalization of the legislation with respect to these activities At the beginning of this period abortion was granted only on the basis of clinical indications but by and large observance of this rule was complied with quite liberally A statute which granted freedom of choice in abortion was introduced in 1970 for all women over 38 years of age and for women with four or more home living children and permission for abortion to all women pregnant less than 12 weeks was established on 1/10 1973 At the same time the regulations for sterilization were also liberalized so that free determination for sterilization was granted to both men and women over 25 years of age on 1/10 1973

It seems quite probable that this liberalization has influenced the choice of contraceptive methods since with all other factors constant relaxed restrictions on abortion and sterilization might be expected to be accompanied by less caution with respect to contraception If that expectation were correct an absence of liberalization of the statutes ought to have produced a still greater shift toward more effective means of contraception than was observed

In our examination of the influence of socioeco-

IX *Frequency (in per centage) of sterilization in relation to the number of pregnancies in ten year age ...s*

...roups	No of pregnancies 0	1	2	3	4	5	6	No
1969								
39 years	2 9	0 8	0 4	1 3	3 6	10 1	17 2	181
49 years	3 4	0 5	0 4	1 7	4 8	11 5	15 5	247
1974								
39 years	6 8	3 4	2 5	1 5	6 9	13 9	29 3	355
49 years	14 7	12 3	10 2	13 6	16 6	26 7	32 1	938
...no								1 721

nomic conditions on the use of contraception we found this factor to have an extraordinarily large effect. As the social level decreased, more ineffective forms of contraception were used. There is a highly significant difference between groups 7 and 8. Svalastoga and Wolf (15) state that group 8 is composed of individuals completely deprived of education and with a low income, and that they constitute 25 per cent of the population. There can thus be two reasons for the use of less efficient forms of contraception, one being a lack of comprehension of the concept of contraception and the other a lack of economic ability to purchase contraceptives. In Denmark during the investigation period, guidance in questions of contraception was dispensed without charge, whereas the implements of contraception must still be paid for by the consumer.

Other authors have studied contraceptive habits in women, mostly with younger age groups (7, 8, 9, 12, 14), but one investigation (16) concerned the same age groups as in the present work. A common tendency perceived in all of these investigations was the surprisingly large number of women who failed to use contraception, of whom a large proportion were women from disadvantaged conditions. The employment of inefficient contraception or its absence varied from 20–66 per cent in these studies.

The fact that so many women in group 8 have been sterilized is remarkable but understandable. Before the implementation of the above mentioned statutes permitting greater freedom of choice in sterilization there was quite liberal position toward gynecological intervention resulting in infertility, and this position was particularly pronounced with regard to women of disadvantaged social status. In addition, many women in group 8 had given birth to a large number of children and this in itself served as a reason for sterilization. Finally, contraception by means of sterilization is cheap and effortless.

The attitude toward contraception by the nulligravida depicted in Tables VIII and IX can perhaps be explained by the following reasoning. It is quite likely that these women, who were never able to become pregnant, harbour a strong desire to do so, and thereby abstain from contraception. It is also possible that these women believe themselves to be infertile due to the absence of earlier pregnancy, and thus use no contraception. The fact that so many nulligravida were sterilized should not be interpreted as evidence that sterilization was performed to achieve infertility, but rather that they have undergone a gynecological operation of one type or another, not recorded [illegible] investigation, which has caused them to be [illegible] manently sterile.

The significant decrease in the use of contra[illegible] with increasing age can possibly be interpreted [illegible] belief in these women that their fertility dec[illegible] ageing, or even that they are infertile, [illegible] they reject contraception or utiliz[illegible] les[illegible] methods.

This investigation during an 8-year [illegible] agreement with other work, has found an [illegible] utilization of contraception and a d[illegible] wards increased use of more effecti[illegible] meth[illegible] can be ascribed to the expanded d[illegible] mation about contraception, and th[illegible] more and newer types of contraceptives ha[illegible] aged individuals who previously abstained fr[illegible] Unfortunately, the increase in utilization [illegible] adequate and this study had detected a [illegible] tilt, since the segment of the population wh[illegible] greatest need for effective family planning [illegible] themselves most poorly against unwanted [illegible] tion.

In conclusion, increased information abo[illegible] ception and a possible economic subsidy [illegible] ly disadvantaged is recommended, as w[illegible] ued research and development in mor[illegible] means of contraception (11) with h[illegible] socia[illegible] tability.

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1982

Date	Place	Name	Office
1980			
September 2–3	Barcelona Spain	Congreso Europeo Perinatal	VII Congreso Europeo de Medicina Perinatal Apartado de Correos No 29015 Barcelona Spain
September 2–5	Barcelona Spain	7th European Congress of Perinatal Medicine	Congress secretariat Apt de Correos 29015 Barcelona Spain
September 2–6	Berlin Germany	6th International Congress of Psychosomatic Obstetrics and Gynecology	Ass Prof Dr M Stauber Frauenk Charlottenburg der FUB Pulsstr 4 D 1000 Berlin 19 W Germany
September 4–7	Kiawah Island Charleston SC	International Symposium on Carcinoma of the Cervix Biology Etiology & Diagnosis	E S E Hafez M D OB/GYN State University Medical Res B'g 550 E Canfield Detroit MI 48201
September 15–16	Bologna Italy	First International Symposium on Recent Advances in Prenatal Diagnosis	A C Assistanza Congressi Via P Palagi 21 – 40138 Bologna Italy
September 22–28	Varna Bulgaria	3rd International Colloquium on Physical and Chemical Information Transfer in Regulation *of Reproduction and Aging*	Bulgarian Academy of Sciences, J G Vassileva Popova *c/o Dept of Biophysics* 113 Sophia Bulgaria
September 24–26	Kiel West Germany	International Symposium on Fertilization and Artificial Insemination	Priv Doz Dr L Mettler Frauenklinik der Universitet Kiel Hegewischstrasse 4 D-2300 Kiel 1
Sept Oct 27–5	Oxford England	Endocrinology of Human Infertility New Concepts	Leslie Nies Symposia Manager Ser Symposia 11 Brooks Drie Braintree MA 02184 USA
Sept Oct 29–1	Freiburg Germany	International Congress on Endocrinology of Human Infertility	C Ferrari M D P O Box 995 Milan Italy
Sept Oct 29–3	Boston MA USA	Gynecologic Endocrinology and Infertility	Harvard Medical School D of Continuing Education 25 Shattuck Street Boston MA02115 USA
September 30	London England	Anti androgen therapy for hirsutism	Symposium Secretary Inst of Obstet Gynaecol Queen Charlotte s Maternity Hospital Goldhawk Road London W6 OXG England
October 3–5	New Delhi India	3rd International Seminar on Maternal and Perinatal Mortality Pregnancy Termination and Sterilization	Hon General Secretary The Fed of Obstetric & Gynecological Societies India Purandare Griha 31/c Dr N A Purandare Marg Bombay 400 007 India
Oct Nov 23–3	San Marino Italy	The Gonadotropins Basic Science and Clinical Aspects in Females	Leslie Nies Symposia Manager Ser Symposia 11 Brooks Drive Braintree MA 02184 USA
November 14–17	Madrid Spain	7 Congrès Européen de Medecine Perinatale	Professor de la Fuente Maternidad de la Ciudad Av Generalissimo 177 Madrid
November 18–23	New Orleans LA USA	AAGL Ninth Annual Meeting Clinical Symposium on gynecologic endoscopy	American Association of Gynecologic Laparoscopists 11239 South Lake Boulevard Downey California

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STEROID 16α HYDROXYLASE FROM HUMAN FETAL LIVER INHIBITION BY STEROIDS

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ract The 16α hydroxylase system in fetal liver which dehydroepiandrosterone (DHA) or pregnenolone as rate was apparently inhibited by various endogenous ynthetic steroids DHA pregnenolone their sulfates stenediol androstenetriol estrone estradiol 17β eth stradiol and chlormadinone acetate The inhibition ants (Ki) towards DHA were as follows pregnenolone 1 DHA sulfate 13 μM pregnenolone sulfate 21 μM stenediol 16 μM androstenetriol 53 μM estrone 32 stradiol 17β 75 μM ethynylestradiol 22 μM and chlor none acetate 27 μM The Ki values towards pregneno ere DHA 6 3 μM DHA sulfate 8 3 μM pregneno ulfate 3 9 μM androstenediol 8 7 μM androstenetriol M estradiol 17β 15 4 μM and ethynylestradiol 16 0 espectively The reaction products 16αOH DHA and H pregnenolone showed little inhibitory effect upon α hydroxylase

lation of steroid production by steroids has been nstrated both *in vivo* and *in vitro* Corticoids administered to the pregnant patient or to the in utero are known to suppress the estrogen lev the mother (1 2) Placental 3β hydroxysteroid drogenase activity towards DHA was inhibited dogenous steroids such as 4 androstene 3 17 and progesterone (10) Similarly 3 sulfatase ty towards DHA sulfate was suppressed by pro one and estradiol 17β(9) Little information is ntly available about the controlling mechanism roid metabolism in the human fetal liver which tes a major portion of 16α hydroxylated ster o the feto placental compartments

present study was undertaken to investigate s which may modify the activity of 16α hyd se in the human fetal liver *in vitro*

MATERIALS AND METHODS

active steroids [4 ^{14}C] DHA (58 8 mCi/m mole) and] pregnenolone (55 7 mCi/m mole) were purchased New England Nuclear Corp Boston Mass Before use they were purified by thin layer chromotography (TLC) Non radioactive steroids were obtained from E Merck (Darmstadt Germany) Steraloids Inc (Wilton N H U S A) or Sigma Chemical Co (St Louis Missouri U S A) Cofactors were purchased from Oriental Co (Tokyo Japan) Silica gel GF $_{254}$ was obtained from E Mer ck All chemicals used were of analytical grade

Tissue Preparation Liver was obtained from human fetuses which had been aborted at midtrimester of pregnancy for socio-economic reasons The tissue was dissected out imme diately following delivery of the fetus weighed minced and homogenized in a loose fitting Teflon glass homogenizer in ice cold 0 25 M sucrose solution buffered with 0 05 M Tris HCl at pH 7 4 The homogenate was centrifuged at 10 000 × g for 20 min and the supernatant was then centrifuged at 105 000 × g for 60 min The precipitate was resuspended in 0 25 M sucrose Tris buffer and again centrifuged at 105 000 × g for 60 min The precipitate (the microsomal prepara tion) was stored at − 80 C until used The protein concen tration was measured by the method of Lowry *et al* (5) The 16α hydroxylase activity was stable under these conditions for at least 6 months

Incubation The microsomal preparation of the liver was in cubated with either [^{14}C] DHA or [^{14}C] pregnenolone Each radioactive steroid substrate (0 05 μCi per incubation flask the various specific activities were prepared by adding non radioactive substrate 2 0–50 0 n moles of DHA or 0 5–20 0 n moles of pregnenolone) and the steroid inhib itor to be tested were dissolved in a drop of propylene glycol in an incubation flask together with 0 2 μmoles of NADPH The microsomal fraction equivalent to 10 mg of liver tissue (0 067 mg protein) was then added to start the incubation the final volume was brought to one ml with 0 05 M Tris HCl buffer (pH 7 4) Incubations were carried out for 6 min for [^{14}C] DHA and for 10 min when [^{14}C] pregnenolone was the substrate The incubation flasks were shaken constantly in a Dubnoff incubator at 37 C under an atmosphere of O_2 (95 per cent) and CO_2 (5 per cent)

Under these conditions a linear relationship between the time of incubation and the rate of 16α hydroxylated pro- ducts formed was established for at least 15 minutes At the end of each incubation period 5 ml of dichloromethane was added to the flask and shaken vigorously to terminate the reaction and to extract steroids

Separation Quantitation and Identification of Metabolites The incubation mixture was extracted with a further 5 ml of dichloromethane Carrier steroids (75 μg each) were added

Table I *Specific activities of 16αOH DHA and 16αOH pregnenolone (dpm/mg) after repeated crys[illegible] with carrier The solvent used throughout was methanol*

Metabolites formed	Before crystal lization	1st crystal	2nd crystal	3rd crystal	4th crystal	Mo[illegible]
16αOH DHA	2 132	2 263	1 890	2 011	2 036	2 0[illegible]
16αOH pregnenolone	1 274	1 110	1 165	1 079	1 099	1 0[illegible]

to the combined extracts which were then subjected to ascending TLC in the solvent systems cyclohexane-ethylacetate (1 1 v/v) and benzene-methanol (9 1 v/v) The former system was used to separate metabolites of DHA and the latter those of pregnenolone Each thin layer plate was developed twice to ensure good separation The carrier steroids were visualized by exposing the plate to iodine vapor The stained spots were scraped off placed in scintil lation vials with 0 3 ml of methanol and 10 ml of scintilla tion fluid containing 4 g of PPO and 0 05 g of POPOP per liter of toluene was added Radioactivity was measured with a Packard Tri Carb Liquid Scintillation Spectrometer (Model 3330) The counting efficiency was about 88 per cent for ^{14}C and 55 per cent for ^{3}H

The metabolites were identified by their mobility on TLC and by recrystallization to constant specific radioactivity with authentic steroids The total radioactivity recovered in the 16α hydroxylated metabolites and unchanged substrates was 88 2±0 58 per cent (mean±S E) for DHA and 91 1±0 83 per cent for pregnenolone The conversion rate to a given metabolite was calculated by dividing the activity found in the metabolite by the original activity of the labell ed substrate No correction was made for losses during ex

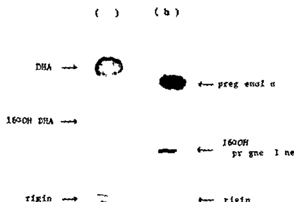


Fig 1 Autoradiograms of TLC plates of the metabolites formed from DHA and pregnenolone in incubation ex periments with fetal hepatic microsomes DHA (50 0 μM) and pregnenolone (10 0 μM) were incubated for 6 min with hepatic microsomes (0 268 mg protein) These conditions provided the maximum reaction rates for both substrates (a) ^{14}C DHA incubated as a substrate (b) ^{14}C pregnenolone incubated as a substrate

traction and purification The reaction rat[illegible] 16α hydroxylase was expressed as n moles of [illegible] formed under the conditions described Statistic[illegible] tion of the inhibitory effects of steroids was carried [illegible]cording to the method of Cleland (3) and by mean[illegible] Student s t test

RESULTS

Identification of the Products Fig 1 shows the [illegible]radiograms of the thin layer plates on which the [illegible]tabolites of radioactive DHA and pregnenolone [illegible] separated A radioactive spot corresponding [illegible]thentic 16αOH DHA was observed as the ma[illegible]tabolite of [^{14}C] DHA Similarly 16αOH [illegible]lone was the major metabolite when [^{14}C] pre[illegible]lone was incubated with the liver mi[illegible] Radiochemical purity of each of these met[illegible] was confirmed by crystallization to constant sp[illegible] activity with the authentic compound (Table I)

Effect of Substrate Concentration Fig 2a sh[illegible] relationship between concentration of DHA [illegible]ed and the amount of 16α hydroxylated pr[illegible] formed *The apparent Km value* calculated b[illegible] method of Lineweaver and Burk was found [illegible] 6 81 ± 0 68 μM A similar study was performed [illegible] pregnenolone and the apparent Km value was [illegible] 0 70 μM (Fig 2b)

Table II shows the inhibitory effect of st[illegible] which are either normally found *in the fetal* c[illegible]tion or are widely prescribed synthetic prepar[illegible] upon the 16α hydroxylation of DHA and pre[illegible]lone 16α hydroxylation of DHA was su[illegible] significantly by DHA sulfate ($p<0\ 05$) [illegible]lone ($p<0\ 05$) pregnenolone sulfate ($p<0$ [illegible] drostenediol ($p<0\ 05$) and androstenetriol [illegible] at final concentrations of 10 μM the inhibi[illegible] stants (Ki) calculated from double reciprocal [illegible] were 13 22 21 16 and 53 μM respectively [illegible]sion of pregnenolone to 16α OH pregnen[illegible] also significantly inhibited by DHA ($p<0\ 05$) [illegible] sulfate ($p<0\ 05$) pregnenolone sulfate ([illegible]

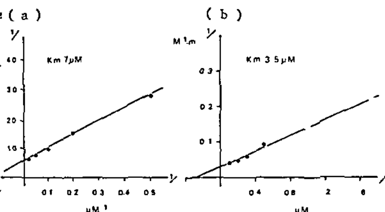


Fig 2 Relationship of the substrate concentrations and the amount of product formed (a) Lineweaver Burk plots for DHA Increasing concentrations of DHA were incubated with fetal hepatic microsomes (equivalent to 0 067 mg protein per flask) for 6 min (b) Lineweaver Burk plots for pregnenolone The incubation time was 10 min under the same conditions as in (a)

…ostenediol ($p<0\ 05$) and androstenetriol ($p<$ … the apparent Ki values being 6 3 8 3 3 9 8 7 … 4 7 μM respectively

…e reaction products 16α OH DHA and …OH pregnenolone showed a slight inhibitory ef… …on 16α hydroxylation the Ki values were 76 μM … 00 μM towards DHA and 45 5 μM and 80 2 μM …ds pregnenolone although the effects were not …tically significant

… the other steroids tested only estradiol 17β (Ki … μM towards DHA and 15 4 μM towards preg…lone) and ethynylestradiol (22 and 16 μM) sig…ntly suppressed the 16α hydroxylase (Fig 3) …ne and chlormadinone acetate showed an in…ory effect only towards DHA (Ki = 32 and 27 …vely) Other steroids had no effect on the …ydroxylation of either substrate

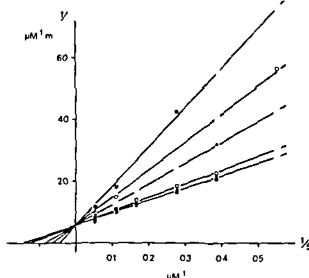
DISCUSSION

It has been demonstrated by *in vitro* studies of human placental tissue that the sulfatase towards DHA sulfate was inhibited by steroids normally found in the placenta or cord blood (8) This may be a mechanism for controlling placental estrogen synthesis from conjugated precursors In the human testis estradiol 17β had an inhibitory effect on 3β hydroxysteroid dehydrogenase as well as 4 5-ene isomerase activity *in vitro* (11) Similarly 17β hydroxysteroid dehydrogenase in the human testis was found to be enhanced by the addition of the 17β hydroxysteroids and slightly inhibited by the addition of DHA sulfate and androstenediol 3 sulfate (6) These data are all concerned with the endocrine organs producing hormones and they suggest an autoregulatory mechanism by steroids on the formation of steroid hormone

… II *Inhibitory effect on 16α hydroxylation by various steroids The inhibition constants Ki are given in … or DHA and pregnenolone respectively*

…ounds	Concentration (μM)	Substrate DHA	Pregnenolone
	10 0		6 3
…sulfate	10 0	13	8 3
…enolone	10 0	22	
…enolone sulfate	10 0	21	3 9
…ostenediol	10 0	16	8 7
…ostenetriol	10 0	53	14 7
…H DHA	50 0	76	45 5
…H pregnenolone	50 0	100	80 2
…sterone	50 0	99	69 0
…ne	50 0	32	122 3
…diol 17β	50 0	75	15 4
…l	50 0	318	162 0
…ylestradiol	50 0	22	16 0
…anol	50 0	131	
…hindrone	50 0	91	
…madinoneacetate	50 0	27	64 1

… 05



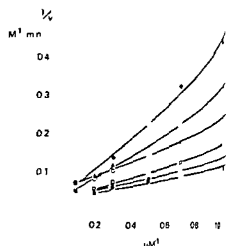


Fig 3 Inhibition of 16α hydroxylation of DHA and pregnenolone by estrogens The incubation was carried out for 6 min for the substrate ^{14}C DHA (a) and 10 min for ^{14}C pregnenolone (b) Inhibitors used ○—○ estrone — estradiol 17β □—□ estriol ■—■ ethynylestradiol ▲—▲ mestranol They were all added to the m b media at the concentration of 50 0 μM

The present study deals with the human fetal liver which is not an endocrine organ in the strict sense However it is well documented that the fetal liver is the principal site of 16α hydroxylation in human pregnancy (7 4) and the conditions used in the pre sent work are optimal for detailed studies on the 16α hydroxylation reaction

Among various steroids added to the incubation media progesterone had no significant effect on 16α hydroxylase but androstenediol acted as a competi tive inhibitor towards the hydroxylation of both DHA and pregnenolone It may therefore be postul ated that androstenediol plays an important role in the autoregulatory mechanism for the production of 16α hydroxylated steroids in the human fetus On the other hand 16α OH DHA and 16α OH pregneno lone which are the products of the hydroxylation studied showed less inhibitory effect on the 16 α hydroxylation so that a negative feedback regulator y mechanism by the products does not seem to be demonstrable in the fetal liver

Estrone estradiol 17β and ethynylestradiol appar ently suppressed the 16α hydroxylase activity The in hibitory effect of estrone on the formation of 16α OH DHA was more pronounced than that of estrad iol 17β On the other hand estradiol 17β was a more potent inhibitor than estrone when pregnenolone was the substrate indicating that the 16α hydroxylase may have different recognition sites towards D and pregnenolone

The inhibitory effect of ethynylestradiol on hepatic 16α hydroxylase activity was grea than that of the two naturally occurring estrogens while mestranol was almost ineffective This fa vides further support for the assumption that the hydroxylase system in the human fetal liver a nished with more than one binding site to enzyme substrate complexes

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following trivial names are used

droepiandrosterone (DHA)	3β hydroxy 5 androsten 17-one
enolone	3β hydroxy 5 pregnen 20-one
stenediol	5 androstene 3β 17β-diol
stenetriol	5 androstene 3β 16α 17β triol
ylestradiol	17α-ethynyl 1 3 5(10)-estratriene 3 17β-diol
anol	3 methoxy 17-α-ethynyl 1 3 5(10)-estratrien 17β-ol
hindrone	17α-ethynyl 17β hydroxy 19-nor-4-androsten 3-one
madinone acetate	6-chloro-17α hydroxy-4 6-pregnadiene 3 20-dione acetate
methasone	9 fluoro-11β 17α 21 trihydroxy 16α methyl 1 4-pregnadiene 3 20-dione
usolone	11β 17α 21 trihydroxy 1 4-pregnadiene-3,20-dione

ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1982

Date	Place	Name	Office
Continuation			
November 20 – 22	Barcelona Spain	Symposium International Sobre Monitarizacion Prenatal	Instito Dexeus Srtas M Luis Ar… Ana Baldrich c/Paseo de la … 67 Barcelona 17 Spain
November 22 – 25	Bombay India	First National Congress on Hormones and Human Reproduction	Mahendra N Parikh Organizing Secretary Dr Jhaveri s Hospital … Lady Hardinge Road Bombay 40… India
December 1 – 4	Kairo Egypt	Second Congress of the International Society for the Study of Hypertension in Pregnancy	Docent Hjördis Robbe Dept of Obstet and Gynecol Karolinska Hospital S-104 01 Stockholm 60 Sweden
December 1 – 12	Melbourne Australia	Seventh UICC Training Course in Cancer Research	Dr A W Burgess UICC Course, The Walter and Eliza Hall Institu… Royal Melbourne Hosp P O 3… Victoria Australia
1981			
January 26 – 31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Congr Admin 31600 West Chicago Livonia, MI … USA
March 14 – 18	Atlanta USA	37th Annual Meeting of the American Fertility Society	The American Fertility Society 1608 13th Avenue South Suite 1… Birmingham Alabama 3520… US…
March 22 – 26	Berlin West Germany	IIIrd World Congress of Human Reproduction	Dozent L Mettler Frauenklin… Hegewischstr 4 D 2300 Kiel 1
April 15 – 17	Gorizia Italy	International Course on Ultrasound in Obstetrics	Filippo Destro Organising Secreta… Dept of Obstetrics and Gynecolog… City Hospital Via Vittorio Veneto… 34170 Gorizia Italy
June 9 – 12	Ostend Belgium	Third International Congress on the Menopause	The International Menopause Soci… 8 av Don Bosco 1150 Brussels
August 24 – 28	Cambridge England	XIII Acta Endocrinologica Congress	Conference Services Ltd XIII Ac… Endocrinologica Congress 3 Bute … London SW7 3EY England
Sept-Oct	Athens Greece	VIth European Congress on Sterility (ESCO)	Sekretariat Prof Dr K Semm F… klinik der Universität Kiel Hegew… strasse 4 2300 Kiel 1 West Germa…
October 25 – 31	Melbourne Australia	Eight Asian Congress of Obstetrics and Gynecology	The Organizing Secretary VIIIth A… Congress of Ob tetrics and Gynaec… G P O Box 2195T Melbourne 30… Victoria Australia
1982			
October 17 – 22	San Fransisco CA USA	Xth World Congress of Gynecology and Obstetrics	Xth World Congress of Gynecolog… Obstetrics c/o The American Coll… Obstetricians and Gynecologists, One East Wacker Drive Su…e 2… Chicago Illinois 60601 USA

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EFFECT OF DIHYDROERGOTAMINE ON COAGULATION FACTORS AND COMPONENTS OF THE FIBRINOLYTIC SYSTEM

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ract Dihydroergotamine (DHE) was given to 20 gyne gical patients 0 5 mg i m preoperatively and again twelfth hour for 7 days No cases of thrombosis oc d as judged by the ^{125}I fibrinogen test Increased con ations but within normal range were found for fibrin factor VIII activity and related antigen plasminogen antithrombin III and decreased concentration for macroglobulin The fibrinolytic activity of the wall of a rficial hand vein was not suppressed which otherwise rs postoperatively Together with the increased concen on of antithrombin III this might explain the potentia ffect of DHE on prophylactic treatment with low-dose rin

use of dihydroergotamine (DHE) combined with dose heparin has been reported to reduce the fre ncy of postoperative venous thrombosis and to be rior to low dose heparin alone as evaluated by ^{125}I fibrinogen uptake test (7 21 22) Various anisms of the effect of DHE have been propos such as improvement of the peripheral venous d flow due to venotonic effects of DHE (10 11 20) Sagar *et al* (21) found that the plasma rin levels in patients receiving DHE and heparin significantly higher than in those receiving he n alone Kakkar (9) found heparin combined with to produce a pronounced rise in the activity of hrombin III this factor is known to be of ficance in thrombotic disease (1)

he question also arises whether DHE might in ce the fibrinolytic activator content of the vein l wall which is an important link in the nolytic defence system and found to be defective e majority of patients with recurrent thrombosis

e therefore studied the effect of DHE on the ulation factors and fibrinolytic components in ng the fibrinolytic activator content in biopsy imens of the wall of a superficial vein of the d

MATERIAL AND METHODS

The study consisted of 20 healthy women with a mean age of 59 7 years (range 49–76 years) All patients had been in formed of the aim of the study and gave their full consent All the patients had been operated on for non malignant disease or uterine prolapse The operation was performed under general anesthesia and the blood loss during the operation never exceeded 500 ml for which reason no blood transfusions were necessary DHE 0 5 mg was given in tramuscularly 3–4 hours preoperatively and then every twelfth hour for 7 days

Diagnosis of deep vein thrombosis Each patient received 100 μCi ^{125}I fibrinogen intravenously the day before opera tion and external scanning with Eberline detector was per formed over both legs at 10 different points preoperatively and then 1 3 5 and 7 days after the operation

Laboratory methods Blood samples and venous biopsy specimens were taken preoperatively and on the seventh postoperative day The following determinations were made

Fibrinogen The blood was collected with epsilon aminocaproic acid (EACA) and the fibrinogen was measured using the method of Nilsson & Olow (14) Normal range 0 2 to 0 4 g/100 ml

P & P-complex (prothrombin + factor VII + factor X) was measured using the method of Owren & Aas (17) Normal range 80 to 120 per cent

Factor V levels were measured using the method of Wolf (24) Normal range 80 to 120 per cent

Factor VIII (AHF) activity was estimated according to Nilsson *et al* (13) Normal range 60 to 160 per cent Factor VIII antigen was determined according to Holmberg & Nilsson (5) Normal range 60 to 175 per cent

Factor IX levels were measured using the method of Nilsson *et al* (15) Normal range 60 to 160 per cent

Fibrin/fibrinogen degradation products (FDP) were measured according to the immunochemical method of Nilehn (12) In the presence of EACA and thrombin this method will not show any FDP in serum from normal pa tients in whom a level is below 5 μg/ml

Antithrombin III was determined immunochemically using the method of Fagerhol & Abildgaard (1) Normal range 60 to 140 per cent

Plasminogen was measured using an immunochemical method (3) Normal range 70 to 130 per cent

Inhibitors of urokinase induced plasminogen activation (urokinase inhibitors) The clot method was used (19) Nor mal range 60 to 140 per cent

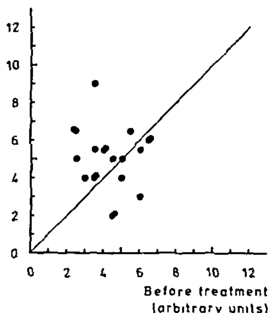


Fig 1 Fibrinolytic activator activity in superficial vein walls before and 7 days after DHE treatment

Alpha₂ macroglobulin was measured with the esterolytic method of Ganrot (2) Normal range 80 to 120 per cent

Fibrinolytic activity in the vein wall (18 23) The principle of the method is as follows Cryostat sections of the specimens collected on glass slides are covered with a plasminogen rich fibrin layer After certain periods of incubation the slides are fixed and stained If plasminogen activators are present they will convert plasminogen into plasmin with digestion of the overlying fibrin layer The digested areas are seen as pale zones in the stained fibrin film They vary in size with the activator activity and can be graded in arbitrary units Normal range 6–10 arbitrary units

Venous biopsy specimens were obtained from the dorsal aspect of the hand under local anaesthesia (Carbocain(R) 0 5 per cent) After a longitudinal incision of the skin had been made a 0 5–1 0 cm segment of the vein was exposed carefully dissected and excised

Statistical methods The level of significance was calculated by Student s t test for paired observations The difference between the fibrinolytic activator content of biopsy specimens was estimated by Wilcoxon s rank sum test

RESULTS

In none of the 20 patients did the ^{125}I fibrinogen test show any evidence of thrombosis Two patients with a slightly increased ^{125}I fibrinogen uptake were also examined using phlebography which similarly showed no signs of thrombosis

All the mean values for the coagulation factors components of the fibrinolytic system were wi... normal range before and after therapy Table Significant changes were noted for fibrinogen, fac VIII activity and antigen plasminogen antithro... III and alpha macroglobulin

The median value of fibrinolytic activator in ... wall was 4 5 (2 5–6 5) arbitrary units before and (2–9) after treatment a slight increase which w... significant Fig 1

DISCUSSION

The results show that the fibrinolytic activator c... tent in the vein wall was unchanged or even sl... increased A low fibrinolytic activity in the vessel is a common defect in patients with thromb... disease (8) Åberg & Nilsson (25) found a decrea... this fibrinolytic activity to be a common postop... tive finding especially after major surgery Our ... dings therefore indicate that DHE counteract... postoperative suppression of the fibrinolytic de... system

In the present study fibrinogen and factor VIII ... creased but still lay within the normal rang... T... changes are in agreement with earlier reports ... they were ascribed to surgical trauma (6)

Antithrombin III has received increasing atte... in recent years as in some families suffering ... severe thrombotic disease low concentrations of ... tithrombin III have been found (1) Saga et al ...

Table I *Coagulation factors and components of fibrinolytic system measured before and 7 days ... treatment with dihydroergotamine (n=20)*

	Before treatment	After treatment†	S D	Si...
Fibrinogen (g/l)	4 1	4 9	0 6	p<...
Factor V (%)	95	93	9 43	n.s.
P & P (p o h mb (factor VIII + factor X))	106	111	15 8	n.s.
Factor VIII (%)				
imm	138	187	4 44	<...
biol	105	160	72 47	p<...
Factor IX (%)	112	121	24 96	n.s.
Antithrombin III (%)	90	97	8 50	p<...
FDP (μg/ml)	1 2	2 4		n.s.
Plasminogen (%)	109	125	1 00	p<...
Urokinase inhibitors (%)	115	122	16 57	n.s.
α macroglobulin (%)	105	97	14 05	p<...

) mean †) 7th day mean

-onstrated that patients who had preoperative an -ombin III activity of less than 70 per cent of nor -had deep venous thrombosis in the postoperative -d Low-dose heparin potentiates the activity of -hrombin III which is the main explanation for -fect in the prevention of thrombosis Kakkar (9) -d heparin combined with DHE to raise the ac -of antithrombin III substantially more than heparin alone Our finding of an increased con -ation of antithrombin III following administra of DHE suggests a synergistic effect of DHE and -rin on the concentration of antithrombin III

-e frequency of postoperative venous thrombosis -ated with the ^{125}I method has been reported to -1 – 18 per cent in a gynecological material (4) -test was performed to check coagulation factors -fibrinolytic components In this small study the -ce of thrombotic complications confirms the -rombotic effect of DHE which might be ex -ed by an increased concentration of antithrom -II and unchanged fibrinolytic activity in the vein

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ANNOUNCEMENT

The VIth International Congress of Psychosomatic Obstetrics and Gynecology will take place in West Berlin September 2–6 1980 The principle theme of the Congress — *Women in a changing society* — is meant to encourage lectures and discussions dealing with socio-psychological characteristics and cultural influences psychosomatic symptoms and illness as well as with the psychotherapeutic potential in obstetrics and gynecology

The Congress program includes plenary lectures delivered by invited speakers as well as short lectures on recent psychosomatic findings In additon to those working groups scientific films and demonstrations are being planned

Languages of the Congress
English French Spanish and German

Information may be received from
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Ass Prof Dr M Stauber
Frauenklinik Charlottenburg der FUB
Pulsstrasse 4
D 1000 Berlin (West) 19
West Germany

Organizational Secretariat
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An International Symposium on **Carcinoma of the Cervix** will be held on Kiawah Island Charleston South Carolina USA September 4-7 1980

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The First International Symposium on *Recent Ad*[illegible] **Prenatal Diagnosos** will be held at the *Pala*[illegible]*o della C*[illegible] *e Dei Congressi* in Bologna Italy on the 15th and 1[illegible] September 1980 The symposium organized by the [illegible] rical and Gynecological Department of the Bologna [illegible] sity and by the F Angelini Research Institute Ro[illegible] include a number of Round Tables on the main a[illegible] prenatal diagnosis

Presidents of the Congress are
Professor P E Polani London England and
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Xth World Congress on Fertility and Sterility The [illegible] tional Federation of Fertility Societies will sponsor the World Congress to be hosted by the Spanish Fertility S[illegible] ty at the National Palace of Expositions and Congres[illegible] Madrid Spain September 20-26 1980

There will be two days for Pre-Congress Symposi[illegible] Post-Graduate Courses followed by a program on the [illegible] lowing themes

Spermatogenesis
- Ovulation

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EFFECTS OF ETHINYLESTRADIOL/D—NORGESTREL COMBINATIONS ON SERUM LIPOPROTEINS

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tract Serum lipoproteins were analyzed in 33 young nen (mean age 22 years) before and after two cycles of tment with one of the following ethinylestradiol/d nor rel combinations (µg/µg) 30/150 50/150 and 50/250 ight but significant weight increase of 1 2 kg was found in the 50/150 group All three hormone combinations similar effects on the lipoproteins Before treatment all ects had normal lipoprotein concentrations Whole m triglyceride (TG) and cholesterol concentrations were significantly affected In the whole group the LDL TG centration increased from 0 24 to 0 33 mmol/l ($p <$ 1) and HDL-cholesterol fell from 1 54 to 1 35 mmol/l 0 001) Smokers tended to have lower HDL-cholesterol non smokers It is possible that HDL reductions for er periods of time may be one of the factors that pro the development of atherosclerotic manifestations in ig women on oral contraceptives

ig

...l contraceptives are often used for several years ing which a woman is exposed to the metabolic ormalities associated with this treatment How oral contraceptives of today contain consider lower concentrations of hormones than some rs ago with less unwanted side effects In 1971 we lied the effects of Anconcene[R] (0 1 mg mes iol + 3 mg chlormadionone acetate) on serum lipo teins (16) After two months the serum triglyc e (TG) concentration had almost doubled and the im cholesterol concentration increased 12 per The TG and cholesterol concentrations rose in very low density lipoprotein (VLDL) low density protein (LDL) and high density lipoprotein)L) fractions Continuing medication with only ormadinone acetate led to normalisation of these ies but not until after six weeks

Wynn *et al* demonstrated less marked serum lipid nges after administration of a low dose prepara containing 30 µg ethinylestradiol + 150 µg d nor rel (21) The mean serum TG concentration in sed by about 10 per cent and serum cholesterol 10 per cent Still such changes of whole serum lip oncentrations do not appear unless the lipoprotein concentrations of TG and cholesterol have been significantly affected (6) We therefore analysed serum lipoproteins in detail in women on low dose oral contraceptives Since combinations of estrogen and progestagens may have complex effects on lipoprotein metabolism three different hormone combinations were chosen

SUBJECTS

The women were recruited from a contraceptive clinic run by the Stockholm County Civil County where they all applied for prescriptions of oral contraceptives The gynecologist who examined them invited them to take part in the study and their informed consent was obtained The recommendations by the Swedish National Board of Health 1977 were followed for exclusion of women for whom oral contraception were considered not to be advisable No woman had used oral contraceptives later than 6 months prior to the present study

Forty-one women (mean age 22 years range 17 29 years) were referred to the Lipid Unit Karolinska Hospital where a fasting blood specimen was drawn for lipoprotein analysis The body weight was recorded and they were asked about smoking and drinking habits At random the women were then given one of three contraceptive preparations for two cycles and were asked to return at that time for another blood sample Both samples were drawn between the 21st and 26th day of the menstrual cycle The patients were evenly recruited to the study throughout one whole year in order to eliminate the influence of seasonal variation on lipid concentrations For unknown reasons 8 women who had come to the Lipid Unit for the first visit did not appear on the second occasion in spite of repeated calls

Three different drugs were used (kindly supplied by AB Recip Stockholm) They contained ethinylestradiol/d norgestrel in the following combinations 30 µg/150 µg 50 µg/150 µg and 50 µg/250 µg

Serum lipoproteins were determined by preparative ultracentrifugation as described by K Carlson (5) After centrifugation at d = 1 006 the top fraction was harvested and called the VLDL fraction Heparin manganese chloride was added to the infranatant which precipitated the B-apoprotein containing LDL fraction The remaining lipoprotein in solution was defined as the HDL fraction The concentration of TG and cholesterol in whole serum VLDL LDL+

Table I *Body weight (kg mean±SEM) before and during oral contraceptive treatment with drugs of various combinations*

Horm comp estr/d norg†	No	Body weight Before	During	Sign diff
30/150	11	62 8±2 2	63 1±2 2	p>0 05
50/150	*9*	*58 2±2 2*	*59 4±2 1*	*p<0 05*
50/250	13	64 5±2 4	64 8±2 4	p>0 05

† ethinylestradiol/d norgestrel (μg) Student s t-test paired data

HDL were determined by Technicon Auto Analyzer methods (3 10) The LDL concentrations of TG and cholesterol were calculated by subtraction The recovery ranged from 90–110 per cent

RESULTS

Thirty three women completed the study There were no major complaints with regard to drug tolerance The body weight before and after treatment is shown in Table I 50 per cent of the women were non smokers whereas 37 per cent smoked more than 10 cigarrettes/day 13 per cent consumed more than one bottle of wine/week (or alcohol in corresponding quantities) The three drug groups were similar with regard to age smoking and drinking habits

Before treatment the lipoprotein concentrations were similar in the three groups (Table II) All women had low to normal serum lipid concentrations and no subject developed hyperlipoproteinemia during treatment The serum concentrations of total TG and cholesterol did not change significantly during treatment with either preparation although there is tendency for TG to rise In the VLDL fra... and cholesterol concentrations were not increase any preparation and the VLDL cholesterol/TG- was unaffected In LDL the TG by about 35 per cent in all three groups (p<0.... The LDL cholesterol concentration did no... In the HDL fraction a slight TG ed after treatment only with the 50/150 The HDL cholesterol concentration fell by value of 12 per cent in all groups (p<0 00... 50/250 and the 30/150 groups significant were found (p<0 001 and p<0 05 whereas the reduction found in the smaller group did not quite reach statistical significa... smokers the mean HDL-cholesterol was 1 44±0 10 mmol/l and for nor 1 60±0 08 mmol/l but this trend was not stat... significant The mean alcohol consumption modest in this group of women and did not atically affect the serum lipoproteins

DISCUSSION

A review of studies on the effects of stero... traceptives on lipid metabolism is confusing (1... designs have been different data from ferent types of steroids have been combined studies the women have not been their own and furthermore the women have been on for periods which have varied from weeks Finally results from studies of postmenopausa... en on hormonal replacement therapy ...

Table II *Triglyceride (TG) and cholesterol (Chol) concentrations (mmol/l mean ±SEM) in the lip... fractions before and during treatment with oral contraceptives of varying hormonal composition*

Horm comp estr/d norg†	VLDL TG	VLDL Chol	LDL TG	LDL Chol	HDL TG	HDL Chol	Total TG	Total C...
30/150								
Before	0 43±0 07	0 23±0 05	0 23±0 02	2 73±0 15	0 13±0 02	1 68±0 08	0 83±0 10	4
During	0 46±0 05	0 28±0 03	0 31±0 02	2 86±0 31	0 14±0 0?	1 43±0 08	0 96±0 07	4
50/150								
Before	0 61±0 12	0 34±0 05	0 26±0 03	2 94±0 10	0 14±0 03	1 37±0 10	1 05±0 13	4
During	*0 61±0 07*	*0 36±0 05*	*0 35±0 02*	*2 92+0 10*	*0 17±0 02*	*1 26±0 10*	*1 17±0 09*	4.
50/250								
Before	0 53±0 09	0 31±0 05	0 25±0 04	2 68±0 23	0 15±0 01	1 52±0 10	0 96_0 14	4
During	0 48±0 06	0 28±0 03	0 33±0 03	2 81±0 16	0 15±0 01	1 34±0 08	1 00±0 09	4
All women								
Before	0 52±0 04	0 28±0 03	0 24±0 02	2 78±0 10	0 14±0 01	1 54±0 06	0 94±0 07	4
During	0 51±0 04	0 30±0 03	0 33+0 01	2 86±0 12	0 15±0 01	1 35±0 05***	1 03±0 05	4

† ethinylestradiol/d norgestrel (μg) Statistically significant differences (Student s paired t test) are indicated p<0 05 ***p<0.0...

other results than studies of young or middle ag on oral contraceptives

n our study the women were their own controls three hormone combinations could be studied er identical conditions The follow up period was y two months However a longer time interval ould probably have led to a considerable drop out these young and symptom free women

n spite of different compositions the three drugs in this study gave similar results Total serum l concentrations did not increase although there a tendency for serum TG to increase in accor ce with other studies (13 17 18 21) In contrast ome of these studies no significant serum choles l reduction was observed (13 18 21) It has been ed that a possible metabolic advantage of these dose oral contraceptives is the fact that they may r the serum cholesterol concentration (21) This ld undoubtedly have been an advantage had the ction occurred in a lipoprotein fraction with rogenic properties However in our study the esterol concentrations in the atherogenic VLDL LDL fractions remained unaffected and the only esterol reduction was found in HDL Since there w general agreement that a low HDL concentra is associated with increased risks for sclerotic manifestations it seems unlikely that DL reduction observed by us is beneficial for women

oking is known to reduce HDL levels and rate alcohol consumtion to increase the HDL ntration (7 8) Since drinking habits were st in these 33 young women no systematic ef of alcohol consumtion could be detected How even in this small group smokers had a trend per cent lower HDL cholesterol levels although eduction was not quite significant

e isolated 35 per cent LDL TG increase during py is a new and uncommon finding An inverse onship between the VLDL TG and the HDL sterol concentrations is well known (15) The reduction would therefore rather have been as ted with a VLDL TG increase The significance e LDL TG increase is difficult to interpret In LDL is considered to be the endproduct of L after TG removal from its core and concomi rearrangement of the surface structures (15) An ed LDL TG increase would rather suggest an ired clearance of LDL TG since in this study the L concentrations remained unaffected

trogens stimulate hepatic TG secretion (9) Im paired lipolysis has also been described and in a re cent study selective impairment of the hepatic lipase activity could be demonstrated (1) On the other hand ethinylestradiol (1 μg/kg body weight and day) caus ed a paradoxical normalisation of the type III broad beta disease hyperlipoproteinemia which is character ized by the accumulation of abnormal VLDL rem nants (12) In that study the LDL lipids were unaf fected and both TG and cholesterol concentrations increased in HDL These estrogen doses were slightly higher than used in our study It is obvious that ef fects on the patients with type III hyperlipoprotein emia may differ greatly from the effects on the low serum lipoprotein concentrations seen in healthy young women It is possible that in our study the estrogenic effects may have been partly counteracted by the norgestrel component of the oral contraceptives

Krauss *et al* have compared lipoprotein levels in 18 users with 19 agematched non users (11) A signifi cant increase was found only of the HDL fraction By detailed fractionation this increase could be located to the denser part of this fraction the so-called HDL_3 However since the 18 women studied had us ed oral contraceptives of seven different composi tions a strict comparison is difficult to perform

Several epidemiologic studies have compared serum lipid levels of hormone users to non users and obtained quite different results The Lipid Research Clinic Program found a 48 per cent increase of the plasma TG concentration in women on oral con traceptives aged 20–24 years (19) The mean plasma cholesterol concentration was 5 per cent higher However these investigators never specifically asked for the exact type of hormone medication

In the Leiden population study the HDL choles terol concentration was about 10 per cent lower in women on oral contraceptives than in non users (2) It is possible that clinical conformity in the Leiden area has led to prescription of similar low dose prepa rations which might explain a more uniform pattern of lipoprotein values

Only in a recent study (Contraceptive Drug Study Kaiser Foundation Health Plan) the importance of the type of oral contraceptive was taken into account in the lipoprotein data analysis (4) These 4 978 wom en supplied information about smoking drinking habits and about the brand and dosage of the hor mone preparation they were using Estrogen users had significantly higher HDL-cholesterol concentra tions than controls In progestin users significantly

lower HDL cholesterol concentrations were found In women on combination drugs the HDL levels varied with the type and dose of the steroids but the general pattern was an increase of HDL cholesterol with increasing estrogen doses and a decrease with increasing dose or potency of the progestin component

The clinical consequences of a reduced HDL cholesterol concentration in this group of young women remains to be elucidated A low HDL concentration is a strong and independent risk factor for the development of atherosclerotic manifestations (14) No longitudinal studies have as yet shown whether lower HDL concentrations will be the cause of the increased risks to develop atherosclerotic manifestations that has been demonstrated in women on oral contraceptives (21) However as pointed out by Arntzenius *et al* in the Leiden study their 40 year old women on oral contraceptives had disturbingly low serum HDL cholesterol concentrations which were similar to the concentrations found in men of the same age group (2) A lowered HDL cholesterol for several years may place women at the same risk level as men for atherosclerotic manifestations

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LOCAL APPLICATION OF KETOCAINE FOR TREATMENT OF REFERRED PAIN IN PRIMARY DYSMENORRHEA

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ract In a randomized double blind cross-over study ffect on referred pain of the local anesthetic ketocaine valuated in 23 women suffering from primary dysmen a Ketocaine was administered in compresses contain g ketocaine in a 10 per cent ethanol solution The in zation comprised two consecutive menstrual periods ng one the patient received ketocaine compresses and ig the other placebo compresses i e compresses with etocaine The compresses were applied to the skin area e the patient experienced the most intense pain

hen receiving ketocaine compresses 19 of the 23 pa s reported good or moderate pain relief The effect was nized within 30 to 60 minutes and lasted for a mean of rs (range 1 5–5 h)

nly four of the patients reported relief of pain when re ig placebo compresses This effect ceased when the presses were removed

general side effects were registered However ema at the site of compress application was more often ved after ketocaine than after placebo compresses

enorrhea is one of the most common ological complaints In the literature figures on revalence of the disorder show wide variation g 3 5 6 8) Preliminary results from a not yet leted study reveal that 15 per cent of school girls years suffer from regularly recurring dysmenor (10)

smenorrheal pain may be the result of hyperac of the uterine muscle and myometrial ischemia itly performed intra uterine pressure recordings althy and dysmenorrhal women support this (1 11) The cause of the uterine hypercontrac is not known but is has been shown that β_2 receptor stimulating agents (11) prostaglandin esis inhibitors (7) and recently calcium in rs (1) can decrease uterine tone and intensity of e contractions in dysmenorrheal women Pain is associated with uterine relaxation

ny women suffering from primary dysmenor localize their pain to the lower back or abdomen There is reason to believe that this pain is referred similar to that occurring in labor (2) In a previous investigation ketocaine a new local anesthetic drug was used to treat referred pain during the early stage of labor (9) The promising results of this study prompted us to investigate the effect of ketocaine in patients suffering from dysmenorrhea

MATERIAL AND METHODS

Twenty three women with primary dysmenorrhea were studied All were well known to the investigators The patients suffered from moderate dysmenorrhea with the pain localized mainly to the back In 9 of the subjects intra uterine pressure recordings verified the presence of uterine hypercontractility during menstrual pain Vaginal examination laparoscopy hysteroscopy and/or hysterosalpingography excluded extrinsic factors as causes for the pain The investigation was performed as a randomized double blind cross-over study At the onset of the menstrual pain all 23 women received ketocaine compresses containing 1 g of active substance or compresses containing placebo i e without ketocaine A description of the compresses and the method of application has been given previously (9)

The investigation involved two consecutive menstrual periods

Procedure At the onset of menstrual pain the patient was admitted to the outpatient department of the clinic After observation for approximately one hour during which the need of pain relief was established compresses were applied to the skin area where the most intense pain was experienced Each compress was left in position for one hour During the time of compress application no analgesics were given

When the compresses were removed the patient s assessment of the effect of treatment was determined by using a simple scale 0 = no effect X = moderate effect XX = good effect

Local effects on the skin such as erythema and edema were looked for and recorded The duration of the effect was estimated by asking the patient to record her degree of pain relief every second hour according to a written schedule She was also asked to record the amount of simple analgesics taken during the two following days

The same procedure was repeated at the next menstrual period

Table I *Effect of treatment of assessed by the patients*

	Good	Moderate	None
Placebo	1	3	19
Ketocaine	8	11	4

Table II *Percental distribution of reported symptoms at the site of compress application*

Symptom	Placebo	Ketocaine
None	52	3
Cold	22	17
Warm	13	34
Burning	0	14
Itch	13	3

RESULTS

As can be seen in Table I 19 of the 23 patients reported good or moderate pain relief after treatment with ketocaine compresses The effect was recognized within 30 to 60 min and lasted in the mean for 3 h (range 1 5 – 5 h)

In contrast only 4 of the patients reported relief of pain when treated with placebo compresses In three of the patients pain relief was reported within 30 min The effect of treatment ceased when the compresses were removed

Neither during treatment with ketocaine nor during the placebo administration were any general side effects observed Local symptoms were reported both during placebo and ketocaine treatment (Table II) It was found that after ketocaine a few patients exhibited a moderate erythema at the site of compress application

During the first two menstrual days the consumtion of simple analgesics was 50 per cent higher in the group treated with placebo compresses compared with that treated with ketocaine

DISCUSSION

From the present study it is evident that ketocaine locally applied to the skin can be used to treat referred pain in primary dysmenorrhea Similar results were obtained in patients suffering from painful labor (9) However as dysmenorrheal pain lasts for a fairly long time and as the effect of the ketocaine compresses generally did not exceed three hours re application has to be performed for effective pain relief during the day Even though no marked local reactions on the skin were observed in the present study re application of the ketocaine compresses may increase the risk of skin reactions (4)

Side effects of the commonly used drugs for treatment of menstrual pain — contraceptive pills prostaglandin synthesis inhibitors and simple analgesics — are fairly common The present results suggest that local treatment of referred pain with ketocaine might be an alternative in patients whos[illegible] are moderate and last for a short time E[illegible] skin reactions no side effects can [illegible] treatment is easily handled by the patient [illegible]

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AMENORRHEA FOLLOWING ORAL CONTRACEPTION

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act In 21 patients with amenorrhea after taking oral iceptives the urinary excretion of estrogens and the a concentrations of LH FSH and prolactin were ined In five of these women the amenorrhea was ac amed by galactorrhea Ten of the 21 patients had had nenorrhea before contraceptive therapy The pro- one test was negative in 9 patients and clomiphene test egative in 10 patients The urinary excretion of estro- ind plasma LH and FSH values were low normal while olactin concentration in group A (amenorrhea with ilactorrhea) amounted to 12 8±2 4 μg/l of plasma and oup B (amenorrhea with galactorrhea) to 85 4±15 8 p<0 01) The pituitary response to 100 μg synthetic H i m was similar to that found in the early follicular of the ovulatory cycle and showed that the pituitary apable of synthesizing and secreting LH and FSH the three women from group A who wanted to be pregnant conceived under the therapy with Clomid ICG In all women from group B in response to del (bromocriptine) therapy administered in 5 mg dose the plasma concentration of prolactin decreased to a il level galactorrhea ceased within 15–62 days and resumed within 38–75 days In three women ry probable that the cycle became biphasic and a pre clomiphene negative patient became a clomiphene ider

I

iorrhea after treatment with combined oral con otives is encountered in clinical practice with in ng frequency In many cases spontaneous ation of the menses and of the ovulatory cycle s however there are patients with persistent tanding amenorrhea who are often very resis o therapy Ten years after the introduction or ontraceptives into clinical practice Whitlaw *et* 966) reported on amenorrhea following cessa of oral contraception Since then many papers been published on the appearance of amenor after using combined oral contraceptives (2 6 7 5) as well as on amenorrhea associated with orrhea (6 10 11)

s paper presents the results of clinical and atory examinations in 21 patients with secon menorrhea which developed after discontinu eatment with combined oral contraceptives

MATERIAL AND METHODS

Twenty one patients with amenorrhea lasting for more than six months including five women with both amenorrhea and galactorrhea were studied In all patients menarche had occurred at the normal age Ten of our 21 patients had had oligomenorrhea before taking contraceptive pills Four teen of the women had already given birth and the remain ing seven were nulligravidae The adrenal and thyroid func tions were normal in all women and plain roentgen rays of the sella turcica revealed no abnormalities The ophtalmolo- gi findings were also normal The following determinations were carried out on all patients the urinary excretion of to- tal estrogens the percentage of superficial cells in the vagi nal smears (pycnotic index PI) plasma LH and FSH con centrations by radioimmunoassay according to Midgley (12 13) and of plasma prolactin by the method of Bryant *et al* (4)

The LH RH test was done by administering 100 μg syn thetic LH RH i m and the plasma LH and FSH concentra tions were measured before as well as at 15 30 45 90 1 0 and 240 min following injection The progesterone test was performed by administering 4×25 mg progesterone cap- roate i m and patients with a positive response were given 100 mg clomiphene daily between the 5th and 9th days of the cycle The patients with a negative progesterone test were also given 100 mg clomiphene daily for five days be ginning from the 10th day after the injection of progester one The clomiphene test was considered positive when the BBT was biphasic with a luteal phase longer than 12 days and the urine pregnandiol level higher than 2 5 mg/24 h be tween the 22nd and 24th day of cycle The patients were divided in two groups Group A consisted of 16 women with amenorrhea without galactorrhea and group B of 5 patients with both amenorrhea and galactorrhea The basic clinical and laboratory findings of the patients are shown in Table I Six of the 21 women had an infertility problem Three pa tients from group A who wanted to become pregnant were given clomiphene and HCG The 5 patients with amenor rhea and galactorrhea were treated with Parlodel (2 bromo- alpha ergocryptine) 5 mg daily over a period of 2 to 5 months The data obtained were statistically analyzed and the significance of the differences was tested using Student t test at the 0 01 significance level

RESULTS

In all patients the basal estrogen concentrations and the pycnotic index were low and plasma LH and FSH concentrations were at the lower limit of normal

Table I *Clinical data of patients with amenorrhea after combined oral contraceptives*

Group	Average age (years)	Average age at menarche (years)	Cycles before contraceptive treatment (normal/oligomenorrhea)	Duration of contraceptive treatment (months)	Duration of amenorrhea (months)	Progesterone test (pos/neg)	Clom (pos/n
A (n=16)	26	14	9/7	20	18	11/5	10 6
B (=5)	29	15	2/3	16	13	1/4	1 4

A = Amnorrhea without galactorrhea B = Amenorrhea with galactorrhea n = Number of patients normal/oligomenorrhea

for the early follicula phase There were no significant differences between estrogen LH and FSH concentrations as between the group with amenorrhea and the group with both amenorrhea and galactorrhea In nine of 21 patients the progesterone test was negative In group B the prolactin concentrations were significantly higher ($p<0\ 01$) than in group A (Table II) In one case galactorrhea appeared during the treatment with oral contraceptives and in the remaining 4 women after cessation of therapy The results obtained by the LH RH test are shown in Fig 1 In both groups an increase in LH and a slightly smaller increase in FSH concentration was noted and the maximal concentrations were observed 60 min following the injection of LH RH The maximal increase in LH concentration was significantly higher in group A than in group B ($p<0\ 01$) while the maximal increase in FSH concentration was approximately the same in both groups All five patients with amenorrhea and galactorrhea were given 5 mg of Parlodel daily and in the three women who wanted to become pregnant the plasma prolactin concentrations were determined weekly All patients from this group measured their basal body temperature In two patients from this group who did not want to conceive an IUD was inserted Fourteen days after the in

itiation of Parlodel therapy prolactin concentra
were normal in all five women galactorrhea
peared within 15 to 62 days in four patients
one patient a slight mammary secretion persisted
beyond the 90th day in spite of the normal prol
concentration In all five patients spontaneous
ing occurred within 38 to 75 days of therapy
ing to the BBT curve a biphasic cycle
in three patients while in two women the BBT
ed a monophasic course even after 9C
the establishment of monthly bl
tion of galactorrhea One of these women
with a previously negative clomiphene test
wanted to become pregnant was given
clomiphene in 100 mg daily doses from the fif
ninth days of the cycle and 10 000 IU of
fourteenth day She did not become
though ovulation was induced (Fig 2)

Parlodel may change a clomiphene non
to a clomiphene responder Two of the
from group A who were treated with
HCG became pregnant but in one patient
could not be induced even with as high a
clomiphene as 150 mg daily over five days

DISCUSSION AND CONCLUSIO

The role of oral contraceptives in the p
secondary amenorrhea is not clear Multip
may play a part in postpill amenorrhea and
irregularity of the menstrual cycle as a pred
factor has been reported by other authors (6
Ten of the 21 patients with postpill amenor
oligomenorrhea before the therapy The
progesterone tests obtained in nine of our 21
indicate severe estrogen deficiency In 10 of
patients the results of the clomiphene test w
tive or impaired (bleeding without ovulation
small group of patients with amenorrhea an
torrhea both the progesterone and clomiph

Table II *Mean basic concentration of the hormones and pycnotic index in patients with amenorrhea after combined oral contraceptives*

Group	TE µg/24 hr	PI	LH U/l	FSH U/l	Prolactin µg/l
A	18 0±6 6	19 4±7 4	12 0±4 2	8 7±2 5	12 8±..4
B	12 8±4 7	15 8±5 6	9 4±2 8	7 3± 5	85 4±15 8
	NS	NS	NS	NS	p<0 01

TE = Total estrogens Values are means ± standard error (normal values in follicular phase without midcycle peak FSH 5–.0 U/l LH 5–15 U/l)

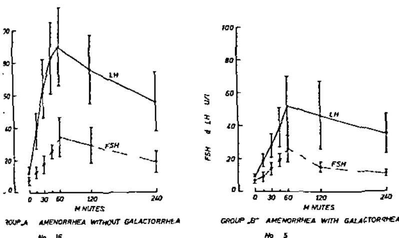
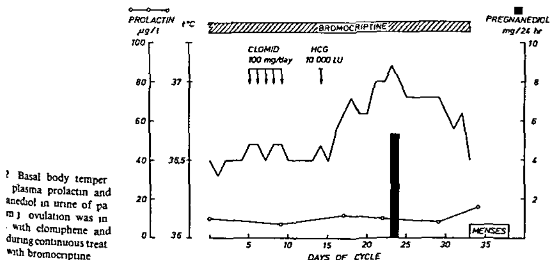


Fig 1 Plasma FSH and LH concentrations before and af ter administration of 100 μg LH RH i m (mean±S E)

negative in four of the five patients Bohnet *et* 3) observed a positive progesterone test in a high entage of women with amenorrhea and an in sed prolactin level and a negative clomiphene in 15 of 17 patients Franks *et al* (9) found that er cent of patients with amenorrhea and hyper actinemia had a negative progesterone test and 97 cent a negative or impaired clomiphene test nblatt (10) succeeded in inducing ovulation with uphene alone in only one of nine patients with aorrhea and galactorrhea while in the remaining it was necessary to give both clomiphene and and in some patients even human menopausal dotropin (HMG) and HCG The pituitary capac synthesize and secrete gonadotropins was nor in both groups of patients Basal LH and FSH concentrations were low normal in both groups the maximal increase in LH following LH RH was sig nificantly higher in group A than in group B ($p<0\ 01$) and the increase in FSH was approximate ly the same in both groups Such a response were observed also in our previous investigation during the early follicular phase of the normal cycle (Smiljanic *et al* 1977 unpublished data) Similar responses have been found by Healy *et al* (11) while Dickey (6) has found a smaller LH increase following LH RH in amenorrheic patients with increased prolactin and low basal estrogen and LH concentrations In these women the response to clomiphene was negative Floersheim Shachar and Keller (8) have demonstrated that patients with the hyperprolactinemic anovul atory syndrome have an adequate pituitary response



? Basal body temper plasma prolactin and anediol in urine of pa m) ovulation was in with clomiphene and during continuous treat with bromocriptine

to synthetic LH RH and a negative response to clomiphene By the administration of Parlodel to patients with amenorrhea and galactorrhea it is possible to achieve supression of the prolactin level restitution of menstruation and cessation of galactorrhea Several other reports have been also published on the successful clinical use of Parlodel in patients with the anovulatory syndrome and hyperprolactinemia (6 8)

Parlodel as an agonist of dopamine stimulates the synthesis of the prolactin inhibiting factor (PIF) in the hypothalamus and acts upon the galactophores of the anterior pituitary by inhibiting prolactin synthesis and secretion (1)

It is a very suitable drug for the treatment of the anovulatory syndrome with hyperprolactinemia and its side effects are neglgible

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HE EFFECTS OF ESTROGENS AND GESTAGENS ON THE URETHRAL PRESSURE PROFILE IN URINARY CONTINENT AND STRESS INCONTINENT WOMEN

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ract The present investigation was performed to study rodynamic effects of hormones on the lower urinary in women Twenty four stress incontinent and 6 conti women were randomly given E_2 and E_3 orally in doses 8 mg per day for 3 weeks Another group of 8 women given a single i m injection of 1000 mg gestagen l the women were examined with simultaneous urethro-metry including urethral pressure profile measure before and after treatment After estrogen treatment ransmission of intraabdominal pressure to the urethra ased Furthermore there was a significant increase in mum urethral pressure and urethral length at rest gestagen treatment no significant changes of the ded parameters were observed

as long been suggested that hormones i e estro and progesterone may affect the female urinary

ost studies on this subject are based on the pa s subjective reports However objective studies cially by intravesical and intra urethral pressure rdings have also been carried out Thus Gitsch Brandstetter (5) in 1954 registered an increased der tone during the follicular phase and a de ed tone during the secretory phase of the men l cycle In contrast the urethral pressure increas uring both the follicular and secretory phases fter treatment with estrogens Slunsky (12 13) rted a considerable improvement of female uri incontinence Walter *et al* (14) found a subject mprovement of frequency urgency and urge in inence after estrogen therapy but no significant ges in urethral pressure or urethral length after reatment In a recently performed investigation *t al* (1979) did not obtain a positive effect on meters of importance for female stress incon ce after treatment with estrogens (4)

e existing conflicting data concerning the value trogen treatment of female urinary incontinence 1 partly be explained by different techniques of tigation and by different doses and types of es ns used in the various studies

The introduction of micro-transducer equipment has made it possible to study simultaneously and with high precision the bladder pressure the urethral pres sure and the urethral closure pressure both at rest and under stress situations (1 2) With this technique most of the measuring artifacts which afflict conven tional pressure recording techniques have been elimi nated and reproducible recordings of high quality can be obtained The present investigation was undertak en to evaluate the micro-transducer technique in the measurement of the effects of high doses of estradiol and estriol on parameters of importance for the main tenance of continence

Further the effects of progesterone on the lower fe male urinary tract seems to be uncertain and few ob jective studies have been performed on this subject The present study therefore also included an investi gation of the effects of high doses of progesterone on the lower urinary tract

MATERIAL AND METHODS

Thirty eight women took part in the study Before the inves tigation they were informed of its purpose and gave their verbal consent The patients were divided into two groups

Group 1 (the estrogen group) consisted of twenty seven postmenopausal and three premenopausal women with a mean age of 61 years (37–78) a mean body weight of 62 kg (49–75) and a mean parity of 1 7 (0–4) Twenty four of the patients suffered from urinary stress incontinence (USI) The remaining six were continent None of them had a cys tocele prolapse or urinary infection

Table 1 *Estrogen treatment*

	MUP Cm H O	CP Cm H O	FUL mm	AUL mm
E (16)	52/55	29/31	24/27	31/36
E_3 (1)	71/74	49/50	28/31	36/39
Total	59/63	37/39	25/28	33/37

mean alues before and after treatm t

Table II *Estrogen treatment Subjective and objective improvement of U S I*

Pat no	Age	Daily treatment	MUP Cm H_2O	CP Cm H_2O	PTR per cent	FUL mm	AUL after [illegible]
7	74	4 mg E_2	36/37	16/9	66/148	25/24	[illegible]
9	70	4 mg E_2	51/43	27/19	81/84	20/27	[illegible]
10	37	8 mg E_3	111/116	91/91	?	37/31	[illegible]
18	66	8 mg E_3	69/55	45/27	?	15/18	[illegible]
19	74	8 mg E_3	65/65	41/37	37/87	34/28	[illegible]
21	80	4 mg E_2	37/49	17/25	89/89	26/29	[illegible]
24	67	8 mg E_3	47/48	19/24	72/83	25/26	[illegible]
30	72	4 mg E_2	31/33	7/5	85/115	12/14	[illegible]
Mean	67		56/56	33/30		24/25	[illegible]

*before and after treatment

Group II (the progesterone group) consisted of eight women all suffering from cystic glandular hyperplasia Six were premenopausal and two postmenopausal The mean age was 49 years (36 – 73) the mean body weight 58 kg (51 – 70) and the mean parity 1 6 (0 – 3) Five of the patients were continent and three stress incontinent Relevant data of the patients are given in Tables II – VI

The patients in Group I were randomly given estradiol valerate (Progynova[R] Schering A G) 4 mg daily for three weeks or estriol (Ovestrin[R] Organon) 8 mg daily for three weeks (Tables II – VI)

The patients in Group II received progesterone (17 hydroxyprogesterone caproate) (Primolut Depot[R] Schering A G) 1000 mg in a single intramuscular injection

Immediately before treatment all patients were examined by simultaneous urethro-cystometry including measurements of the urethral pressure profile (UPP) according to a previously described technique (1 2)

The bladder was filled with body warm saline at a rate of ml/min To simulate a stress situation the patients were requested to cough after every 100 ml of saline had been infused Calculations of the resting pressures were done at a bladder volume of 200 ml taken as a mean of three consecutive recordings Re investigation was weeks after the first examination

Urinary incontinence was recognized in two ways

1 By observation of leakage of urine from the urethral meatus
2 By observation of a negative urethral the recording curve (Fig 1)

Definitions and abbreviations of *calcula*

Bladder pressure (BP) = maximum intravesical

Maximum urethral pressure (MUP)

Closure pressure (CP) = MUP minus BP

Pressure transmission ratio (PTR) = the percentage intra abdominal pressure transmitted to the relation to the bladder pressure on coughing

Functional length of the urethra (FUL) = that urethra where the intra urethral pressure bladder pressure

Absolute length of the urethra (AUL) = that part urethra where the intra urethral pressure atmospheric pressure

Pressure in cm H_2O *Length* in mm

Statistics The differences observed during the study tested for significance by the Student s t test

Table III *Estrogen treatment Subjective but no objective improvement of U S I*

Pat no	Age	Daily treatment	MUP Cm H_2O	CP Cm H_2O	PTR per cent	FUL mm	AUL mm
5	62	4 mg E_2	61/65	37/33	72/76	16/20	[illegible]
12	66	4 mg E_2	64/67	44/47	56/88	26/26	[illegible]
13	52	8 mg E_3	73/76	58/52	?	26/26	[illegible]
16	49	8 mg E_3	89/91	65/67	?	35/38	[illegible]
17	69	4 mg E_2	49/61	25/33	88/70	25/41	[illegible]
20	51	4 mg E_2	65/59	45/39	80/70	24/25	[illegible]
22	52	4 mg E_2	56/61	40/41	?	24/23	[illegible]
23	57	8 mg E_3	59/56	39/36	72/73	29/44	[illegible]
27	54	8 mg E_3	63/77	47/36	?	25/37	[illegible]
Mean	57		64/68	44/42		26/31	

before and after treatment

'e IV *Estrogen treatment No subjective no objective improvement of U S I*

no	Age	Daily treatment	MUP Cm H O	CP Cm H O	PTR per cent	FUL mm	AUL after mm
	66	4 mg E,	41/59	17/23	86/65	16/18	24/29
	50	4 mg E,	43/45	27/29	81/90	21/.0	25/27
	63	4 mg E_2	67/60	37/40	?	.7/27	35/37
	64	4 mg E_2	45/52	17/24	?	19/20	?6/25
	53	4 mg E	36/47	12/22	69/66	26/23	33/30
	45	8 mg E_3	99/120	79/96	?	30/39	33/41
	50	4 mg E_2	61/59	37/39	?	19/25	28/30
ı	56		56/63	32/39		23/24	.9/31

ı e and after treatment

RESULTS

ıp I

hral pressure The MUP at rest increased in ıp I after estrogen therapy from a mean of 59 cm) to a mean of 63 cm H_2O ($p<0\ 05$) (Table I) 'e was no difference between continent and stress ntinent patients Moreover no difference in ef was found between estriol and estradiol treated :nts (Tables I – V)

lder pressure A non significant increase in BP ı a mean of 22 cm H_2O to a mean of 24 cm H_2O observed after estrogen treatment No difference observed between the estriol and estradiol treated :nts in this respect and no difference between :s incontinent and continent patients

'hral closure pressure In accordance with the ll changes in the urethral and bladder pressures urethral closure pressure did not change signifi ly after the estrogen therapy 37 cm H_2O before 39 cm H_2O after treatment respectively

ctional urethral length The FUL increased sig :antly in patients in Group I after estrogen apy from a mean of 25 mm to a mean of 28 mm 0 05) There was no difference between estriol and estradiol treated patients and no difference between continent and incontinent patients

Absolute urethral length The AUL increased from a mean of 33 mm to a mean of 37 mm after estrogen treatment (Table I) This change is significant ($p<0\ 05$) In common with the findings of FUL there was no difference between estriol and estradiol treatments and no difference between continent and incontinent patients respectively

Subjective versus objective effects on U S I Seventeen of 24 patients suffering from stress incontinence reported subjective improvement of their symptoms However there was no correlation between subjective improvement and the improvement of MUP CP or the urethral lengths (Tables II – V)

Intra-abdominal pressure transmission ratio to the urethra In eighteen of the twenty seven patients of Group I the PTR was determined during coughing In six patients the pressure transmission was considerably improved after estrogen therapy (Tables II – V) This improved pressure transmission was highly related to the patients subjective report of improvement Thus all seven patients with improved pressure transmission reported subjective improvement after

le V *Estrogen treatment Continent women*

no	Age	Daily treatment	MUP Cm H_2O	CP Cm H_2O	PTR per cent	FUL mm	AUL mm
	54	8 mg E_3	59/67	39/47	?	33/34	36/37
	58	4 mg E_2	48/59	28/39	105/82	37/46	41/60
	58	8 mg E_3	63/64	43/44	88/83	22/25	29/28
	76	4 mg E_2	64/61	36/33	75/92	33/47	45/58
	65	8 mg E	56/56	.4/32	?	.6/23	41/32
	66	4 mg E,	77/85	61/65	62/89	28/29	31/36
n	63		61/65	38/43		30/34	37/42

,ore and after treatment

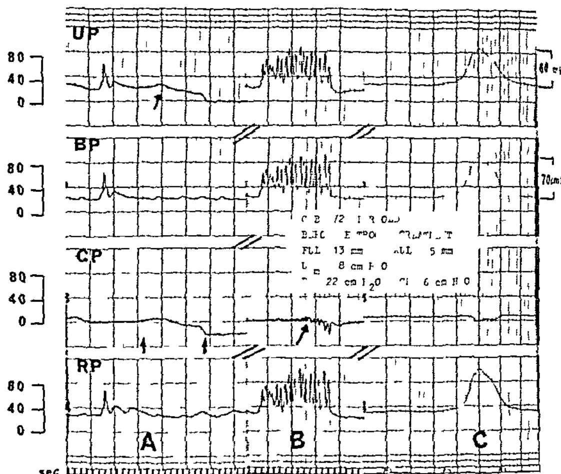


Fig 1 In section A the urethral pressure profile (arrow) in patient G B before estrogen treatment is shown In section B a negative cough profile (arrow) is recorded i e the CP is negative throughout the urethra indicating stress incontinence In section C the urethral transducer is located at the urethral peak pressure A cough resulting in a pressure increase of 70 cm H_2O is transmitted to the bladder and 60 cm H_2O to the urethra i e a urethral pressure transmission (PTR) of 85 per cent The cough result negative CP

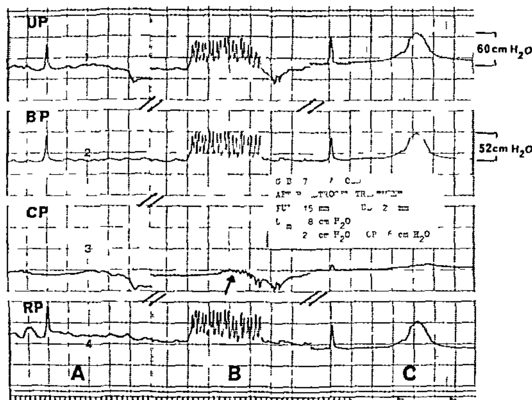
Catheter withdrawal speed in sections A and B 2 5 mm Paper speed 2 5 mm/sec In section C paper sp mm/sec

UP = Urethral Pressure BP = Bladder Pressure CP ure Pressure RP = Rectal Pressure FUL Func Urethral Length AUL = Absolute Urethral Length

Table VI *Gestagen treatment*

Pat no	Age	MUP Cm H_2O	CP Cm H_2O	PTR per cent	FUL mm	AUL mm
A	52	93/76	65/52	?	30/22	45/38
B	48	79/83	43/59	58/52	25/26	40/44
C	48	149/112	109/88	?	37/38	45/43
D	42	81/89	61/69	81/54	26/26	31/30
E	73	80/73	52/49	?	24/27	31/41
F	41	108/108	84/88	107/76	40/40	50/50
G	49	72/84	52/64	?	29/26	35/31
H	36	68/93	60/73	?	34/31	35/40
Mean	49	89/90	66/68		31/30	39/40

before and after treatment



' Same patients as in Fig 1 after estrogen treatment type of recording in the different sections Note that ı unchanged compared with Fig I In spite of this a positive cough profile is shown (arrow section B) The intraabdominal pressure transmission to the urethra has in creased to 115 per cent

ment (Tables I–II) and five were shown to be ctively continent Figs 1 and 2 exemplify the rdings from one of these patients

ıp II (Gestagen treated subjects)

an be seen from Table VI none of the recorded meters changed significantly at rest after gesta reatment In three patients where it was possible etermine PTR this parameter showed lower 's after gestagen treatment in all three patients

DISCUSSION

present investigation has clearly shown that es ns despite high doses over a long period induc nly small changes in important continence pa ters Although an increase in urethral pressure ength was obtained after the treatment it is hard lieve that these small changes alone might imply finitive improvement of urinary incontinence

This suggestion is supported by the observation that there was no significant relation between subjective improvement of the symptoms of urinary stress in continence and the increase of UP and urethral lengths (Tables II–III) The findings in this respect agree with those reported by Walter *et al* (14) and by Ek *et al* (4) but disagree with the results reported by Raz *et al* (9) and by Schreiter *et al* (11)

These different results can be explained by the dif ferent techniques of investigation used The present study was performed with the micro-transducer tech nique whereas the investigations performed by Raz *et al* and by Schreiter *et al* were carried out with the aid of conventional open-end catheters with constant flow

One explanation for the often reported subjective improvement of urinary incontinence after estrogen therapy in postmenopausal women could be that be fore treatment leakage of urine causes a burning sen sation on the atrophic vaginal mucosa Since estrogen

treatment causes a trophic mucosa urinary leakage may be recognized after treatment as less painful or even disregarded by the patients

An important observation in the present study was that in 7 of our patients with subjective improvement of stress incontinence after treatment with estrogen an improved transmission of the intraabdominal pressure (PTR) to the urethra was observed (Tables II–III Figs 1–2) A definite explanation for this cannot be given but it may be due to factors outside the urethra e g improved function of the pelvic floor muscles and the para urethral connective tis sues It is interesting to note that in a recently per formed urethro cystometric investigation of young continent women before and after treatment with danazole it was found that despite considerable de creased plasma estrogens the urethral pressure pro file at rest was almost unaffected whereas the PTR decreased in several of the patients (8)

The findings that gestagens did not affect the pre sent recorded parameters are at variance with the results reported by Raz *et al* (9) but agree with those obtained by Rud (10) In an investigation of young nulliparae during the menstrual cycle this author could not find any significant changes in urethral pressure bladder pressure or urethral lengths related to the changes of progesterone in the plasma

It may be concluded that estrogens in high doses over a long period can improve female stress incon tinence mainly by an improved pressure transmission of intra abdominal pressure to the urethra It must however be emphasized that estrogens in doses used in the present investigation may induce adverse ef fects on other organs e g thromboembolic diseases (3 6) or uterine carcinomas (7) It is therefore debat able whether such therapy is justified in the treatment of patients with symptoms of urinary incontinence alone

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THE IMPACT OF CYTOLOGICAL SCREENING ON THE INCIDENCE OF INVASIVE CERVICAL CANCER

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act A cytological screening program for the early de n and prevention of cervical cancer was started in the y of Malmöhus southern Sweden in 1967

incidence of invasive cervical cancer among women *rly attending* the screening program has been reduced he 10 years to about one quarter of the incidence be he initiation of the program

ures calculated from the whole female population er did not indicate a significant decrease in in e Adequate individual follow up combined with uterized administrative programs and population reg seem to be necessary whenever the effects of a mass ing program are evaluated

ous reports from British Columbia and other give substantial support to arguments for the its of cytological mass screening Statistical sis also indicates that the decrease in incidence rvical cancer is much slower than was expected Sweden each citizen has an individual inden tion number which is in everyday use

1967 a cytological screening program was started uthern Sweden in the county of Malmöhus (M) ogical results as well as some other clinical data previously been reported (13) In the present the impact of this program on the incidence of ive cervical cancer in the M county is reported dition the incidence of cervical cancer in two counties — Kronoberg (G) and Jönköping (F) reported The screening program in these coun as started in 1970

MATERIAL AND METHODS

otal number of women in M county in 1965 was 0 and by 1975 the number had risen to 250 600 All a between 30 and 49 years of age (57 ,00) were invited ticipate (13) and a quarter was invited every year The t follow up runs through 1973 and thus most women een invited twice The female population has been di into three categories those who attended the program (68 per cent) those considering themselves under regular control (18 per cent) and those refusing or ignoring the offer (9 and 5 per cent respectively) In tables and diagrams of the programs from counties F and G only those women who ac tually participated in the screening program are included

In general the screening was completed during the first year During the following years all non negative findings were reevaluated and complementary diagnostic procedures as well as treatment were started

From 1967 to 1973 all patients with invasive cervical can cer in the above mentioned age groups were investigated with particular emphasis on how the diagnosis invasive cancer was obtained in the previous cytological examina tions When appropriate statistical background data from the population registry and data derived from the computer ized screening programs are given

The incidence is given as the average of the four separate 5 year cohorts included in the program The year when the first screening procedure was performed is indicated as year number 0

RESULTS

In Fig 1 the crude frequency of invasive cervical cancer in the county of Malmöhus is given Around 1958–59 cytological examination became widely adopted as a diagnostic method in M county The corresponding peak in the frequency curve is likely to be a reflection of an initial increase in the detection

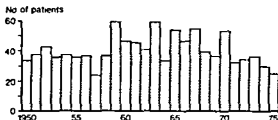


Fig 1 Crude frequency of invasive cervical cancer in coun ty of Malmöhus (M county) since 1950 Cytologic cervical screening was generally adopted around 1958–1960

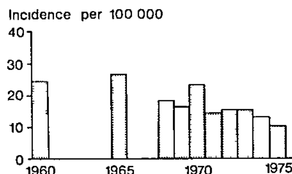


Fig 2 Incidence per 100 000 women of invasive cervical cancer in the whole population of M county

rate However the initiation of the cytological screening program in 1967 was barely detectable and a statistical analysis of the crude data did not demonstrate a significant impact on the frequency of invasive cervical cancer nor could a significant decrease in the incidence in the whole population be demonstrated (Fig 2)

There was however a significant lower incidence in the age groups participating in the screening program as well as among the women considering themselves under regular control (Fig 3)

The incidence of invasive cervical cancer among the abstaining women remained the same before and after the screening

In Fig 4 the incidence figures for the group women attending the screening program are presented Before the year of re screening the curve represents the incidence of invasive cervical cancer in the corresponding year cohorts

The incidence of invasive cervical cancer in the counties M F and G demonstrated a marked decrease a few years after the first screening

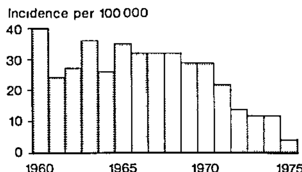


Fig 3 Incidence per 100 000 women of invasive cervical cancer in age group 30–49 years in M county

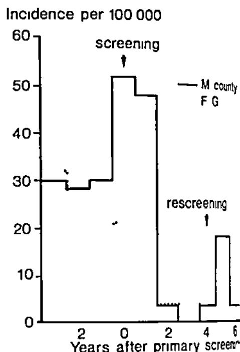


Fig 4 Incidence per 100 000 women of invas cancer among women properly attending the screen gram in M county and in the counties F and G

DISCUSSION

The ultimate goal of the screening program decrease in the mortality rate of cervica been recorded in only few reports (5 19 unreliability of mortality statistics in most obviates any far reaching conclusions on of the screening programs A more useful evaluating the impact of cytological mass programs is the number of women with a diagnosis of invasive cervical cancer Assum the therapeutic results the stage dis biological properties of the malignant d unaltered a decrease in the incidence of the diagnosis should indicate a diminished mortal

The crude frequency of invasive cervical M county has not significantly altered during 25 years The incidence curve did not demons significantly decreasing slope (Fig 2) which cordance with other observations (7 9 12, 14

However if the incidence is calculated of the population that since 1967 has been join the screening program in the county a decrease in incidence is recorded (Fig 3) T in accordance with other reports (2 3 4 8, 15) An even more apparent reduction the screening program if incidence fig

ılated from that part of the population that ac y participated in the program (Fig 4)

ıe reduced incidence could first be noted 3 years the start of the screening program The clear in e found during the first two years is most likely a ction of the increased diagnostic activity The in the incidence of rescreening observed after years is likely to be explained by the number of en who entered the screening program for the time at the rescreening (approximately 30 per Of these the majority moved into the county ıg the interval between the first screening and eening Some women in this group did not res l to the first invitation but joined the program at econd opportunity

us pronounced and rapid decrease in the in ıce of invasive cervical cancer has not been rved by other epidemiologists The difference l be explained by the fact that when incidence uations are calculated from the whole popula he effect cannot be detected before several years elapsed whereas when the calculations are made incidence figures in that part of the population actually was screened the effect is noted early

most western countries the proportion of older n in the whole population is steadily increasing his might contribute further to the weak impact d on the total number of invasive cervical rs in the female population as a whole

me suggest that a reduced incidence might be ex d by fluctuations or a steady decrease caused by own factors influencing the natural history of al cancer (1 6)

e screening program started 3 years later in the ıes F and G and was confined to the same age ıs In these counties identical results were ob d which might indicate that the observed reduc n the incidence of invasive cervical cancer is a of the screening program

CONCLUSION

luced incidence of invasive cervical cancer was l a few years after our cervical mass screening am was started However the impact was detec only in the screened part of the population and ı the total population even 10 years after the ıng program was started Adequate population ıcs combined with a thorough individual fol p seem to be mandatory for evaluating the ef f mass screening programs

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ANNOUNCEMENT

The I an American Congress of Andrology will take place in Mexico City Americana Fiesta Palace Hotel January 26–31 1981

Informations requests for registration and travel information should be directed to

Dr A Negro Vilar
University of Texas Health Science
Center at Dallas
Southwestern Medical School
Department of Physiology
5323 Harry Hines Boulevard
Dallas Texas 75235
USA

Informations requests for registration and travel information should be directed to

Gerald Bagazinski
Congress Administrator
31600 West Chicago
Livonia Michigan 48150
USA

The Third International Congress on the Menopause held in Belgium at the coastal resort of Ostend 9–12 1981 just before the holiday season begins

This Congress will differ from the previous two Grande Motte 1976 and in Jerusalem 1978) in the as the aim in the past was to arrive at a consensus ion this time we shall bravely attempt to confront troversies It will however take the same form as the ones — a number of small workshops rather than meeting attended by everyone

For further information

The International Menopause Society
8 av Don Bosco
B 1150 Brussels
Belgium
Tel (02) 771 95 98 and (02) 771 96 45

The IIIrd World Congress of Human Reproduction is to be held in West Berlin March 22 26 1981

Main topics

- Central nervous system and regulation of reproduction
- Surgical and morphological aspects of reproduction in men and women
- Gonadotrophins and their target tissue
- Beginning of life *in vivo* and *in vitro*
- Experimental embryology of mammals
- High risk reproductive factors in breast and genital cancer
- Influence of the environment and drugs on reproduction
- Free Communications
- Film Festival

Information

Congress Secretariat
Priv Doz Dr L Mettler
Frauenklinik der Universität
Hegewischstrasse 4
D 2300 Kiel 1
West Germany

The Eight Asian Congress of Obstetrics and Gy will be held in Melbourne in October 1981

An exciting and varied programme will be presen cluding expert plenary speakers from Asia Aus other Centres The Congress themes include

- Population Control
- Maternal and Perinatal Mortality
- Trophoblastic Disease
- Gynaecological Malignancy
- Obstetrical and Gynaecological Endocrinology

The official language will be English

Further information may be received from

The Organizing Secretary
VIIIth Asian Congress of
Obstetrics and Gynaecology
G P O Box 2195T
Melbourne 3001
Victoria
Australia

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CASE REPORT

MNIOCENTESIS IN TWIN PREGNANCIES UNDER GUIDANCE OF THE GLUCOSE CONCENTRATION IN AMNIOTIC FLUID

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renatal diagnosis of twin pregnancies it is sary to mark the cavity punctured first to ensure ation of amniotic fluid from both amniotic es Congo red (1) and methylene blue (3 6) have ly been used for this purpose It has been dif to obtain the right form of congo red in Den and methylene blue might be contra indicated se serious complications have been described in its receiving this preparation (4 10)

is difficulty led us to the idea that a biological ance already present in the amniotic fluid might etter marker Glucose is present in the amniotic in the second trimester in a normal concentra f about 0 3–0 6 g per l (8) and even in higher ntrations it is supposed not to harm the fetus se of glucose as a marker requires a quick d for its determination The Dextrostix ne system (Ames) fulfils this requirement

MATERIAL AND METHODS

nciple of the Dextrostix Eyetone system is an elec evaluation of the color shift on a strip which has been sed in the glucose solution The system has been used termination of the glucose concentration in whole (9) and in serum (7) by reduction of the reaction time 0 to 45 seconds For determination in amniotic fluid placed in a small test tube and the Dextrostix is im for 45 seconds With this exception the directions e of the apparatus have been followed strictly

amount of amniotic fluid at the 15–16th week of on is 125–175 ml (5) At this time the injection of 2 ml isotonic glucose into the amniotic cavity will in the glucose concentration 2–3 times By establishing thod we had to be sure that the augmentation of the e concentration takes place quickly and that it re high during the period of the investigation In a pa ho had a provoked abortion we found that the con tion reached a high and constant level within two s and remained unchanged for more than half an

The ultrasonic scanning was performed with the Ecoline ultrasonic apparatus After localization of the placenta the optimal sites of insertion in the uterus were determined by consideration of the fetal echoes The first needle insertion the more difficult one to perform was carried out using a puncture transducer (2) while the second insertion was per formed free hand Fifteen milliliters of amniotic fluid were aspirated by the first puncture and 1 ml of this was used for determination of the glucose concentration Through the puncture needle a suitable amount of isotonic glucose solu tion was injected good mixing being ensured by aspirating and reinjecting before the glucose concentration was reestimated From the second site of insertion 1 ml of am niotic fluid was aspirated for determination of the glucose concentration and if this was in accordance with the physiological level we aspirated 15 ml of amniotic fluid through this puncture needle for prenatal diagnosis Finally it was controlled that the glucose concentration in the first cavity was still much higher than in the second cavity punc tured

Case 1 is a primigravida aged 39 years The indication for the amniocentesis in her 16th week of gestation was aetas The placenta was localized to the posterior wall and the right upper part of the anterior wall The first puncture was performed close to a caput at the upper and left part of the anterior wall of the uterus Clear amniotic fluid was aspirated with a glucose concentration of 0 7 g per l After injection of 2 ml isotonic glucose solution the concentration increased to 1 3 g per l The second puncture was performed close to a caput in the lower and right part of the anterior wall of the uterus and clear amniotic fluid with a glucose concentration of 0 8 g per l was removed Finally the glucose concentration in the cavity punctured first was con trolled and found to be 1 4 g per l Cytogenetic examination of cells from the amniotic cavities showed the normal male karyotypes 46 XY with identical chromosome markers in preparations stained with Quinacrine Mustard and Giemsa for C banding indicating that the fetuses were monozygotic twins The patient gave birth to living male twins in the 39th week of gestation One placenta with a double bladdered septum was found Cytogenetic examination of leucocytes from peripheral blood from the children using the same method as described above showed identical chromosome markers which confirmed that the twins were monozygote

Case 2 is a 4th gravida aged 41 years The indication for amniocentesis in the 15th week of gestation was aetas The

placenta was localized to the lower part of the anterior wall of the uterus and two heads could be demonstrated in the upper part of the amniotic cavity The amniocentesis was performed in a similar manner to that described above The glucose concentration in the cavity punctured first was 0 4 g per l before and 1 85 g per l after injection of 2 5 ml isotonic glucose solution into the cavity The concentration in the other cavity was 0 48 g per l and the control concentration from the first cavity was 1 85 g per l Cytogenetic examination of cells from one cavity showed a normal male karyotype 46 XY and from the other cavity a normal female karyotype 46 XX A comparison of the heteromorphic fluorescent markers in the chromosomes from the female fetus with the chromosomes from the mother in order to exclude the possibility of contamination with maternal cells showed clear differences in chromosome pairs Nos 13 14 15 and 21 The patient has not yet been delivered

CONCLUSIONS

We conclude that the Dextrostix Eyetone system for the determination of glucose concentration is sufficiently fast and accurate for the present purpose The glucose concentration in amniotic fluid after the injection of isotonic glucose remains at a high level long enough for the amniocentesis to be performed These circumstances make the method useful in practice The use of glucose as a marker in amniocentesis in cases of twin pregnancies seems to be without any risk since we are dealing with a biological substance which is already present in the amniotic fluid and which takes part in the normal metabolism of the fetus Therefore glucose is preferable as a marker to the above mentioned dyes

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CASE REPORT

POSTCESAREAN VESICO UTERINE FISTULA

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…act A case of postcesarean vesico-uterine fistula in …ction with a fibrous cord joining the anterior and …ior wall of the bladder is reported The symptoms of …uria and amenorrhoea in the absence of urinary incon…e are explained by reference to the pressure gradients … normally exist in the bladder and the uterine cavity …iology diagnosis and therapy of this and other re… cases are reviewed

…re necrosis following prolonged labor used to … dominant cause of obstetric urinary fistulae nowadays reported only from developing coun… Such fistulae are usually formed between the …r and the vagina In a report by Bird (2) of 70 …ric urinary fistulae 65 were seen after prolong…ior Thirty seven were classified as vesico vagi… 7 as vesico-urethro vaginal and one as a ure…vaginal fistula The remaining 5 were between …adder and the uterus 2 of them were of the … uterine type and developed after lower seg… cesarean section and 3 were of the vesico cer…vaginal type and were secondary to spontane…upture of the lower uterine segment and the …r The bladder was *repaired at the same time as* …ptured uterus but the repair was unsuccessful …sulted in fistula formation

…cer (8) described four different types of fistulae …l to cesarean section the vesico vaginal fistula …sico cervico-vaginal fistula the vesico-cervical … and the vesico uterine fistula The vesico cer…und the vesico *uterine fistulae are usually com…* with amenorrhea and cyclic hematuria (4 6) … fistulae are however not associated with …y incontinence in spite of a patent cervical … Cyclic hematuria has been namned meno… by Youssef (9) The symptoms are more or less …d depending on how long the patient lactates …co-uterine fistulae are rare and as a rule caused … inexpertly performed cesarean section where the bladder has not been properly mobilized and sometimes inadvertently entered Consequently the risk of developing a fistula of this type is increased in patients where previous operations have resulted in a fixation of the bladder to the anterior uterine wall

We report a case of vesico uterine fistula where pre operative investigation also revealed a fibrous bridge between the anterior and posterior wall of the bladder associated with other urologic symptoms

CASE REPORT

A 32 year-old woman who 4 years previously had undergone surgery because of thyreotoxicosis was admitted 4 months after cesarean section complaining of hematuria, frequency and dysuria The patient s first pregnancy resulting in a live male infant was terminated by a transverse lower segment cesarean section because of disproportion between the size of the pelvis and the head of the fetus At operation the bladder was accidentally opened The opening measured 4 to 5 cm and was after delivery closed with two rows of isolated catgut A Foley catheter was used to drain the bladder for 2 weeks In the immediate post-operative period hematuria and albuminuria were seen The patient was discharged after 3 weeks

However frequency and dysuria continued and 2 months later massive hematuria occurred The hematuria gradually disappeared and the urine cleared There was no vaginal discharge and no menstrual blood was noted at the same time as hematuria The patient s complaints resulted in further investigation before admission An intravenous pyelogram (IVP) was normal A cystogram revealed an irregular bladder and a diverticulum was described anteriorly to the right When hematuria was again noted a month later the patient was referred to our department

It was now clearly established that no hematuria had been seen before lactation ceased At the time of her periods which she could feel massive hematuria occurred for a couple of days and then gradually disappeared over the next few days She did not notice any vaginal bleeding

On admission physical examination revealed a nicely healed umbilical incision The vagina was normal The uterus was retroflexed and of normal size Speculum examination showed a small central erythroplakia on the cervix

placenta was localized to the lower part of the anterior wall of the uterus and two heads could be demonstrated in the upper part of the amniotic cavity The amniocentesis was performed in a similar manner to that described above The glucose concentration in the cavity punctured first was 0 4 g per l before and 1 85 g per l after injection of 2 5 ml isotonic glucose solution into the cavity The concentration in the other cavity was 0 48 g per l and the control concentration from the first cavity was 1 85 g per l Cytogenetic examination of cells from one cavity showed a normal male karyotype 46 XY and from the other cavity a normal female karyotype 46 XX A comparison of the heteromorphic fluorescent markers in the chromosomes from the female fetus with the chromosomes from the mother in order to exclude the possibility of contamination with maternal cells showed clear differences in chromosome pairs Nos 13 14 15 and 21 The patient has not yet been delivered

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Cystogram during micturation Oblique projection istolous tract joining the bladder and the uterine cavity rked with an arrow

he absence of urinary incontinence is interesting is patient there was no apparent cervical stricture she menstruated vaginally after the fistula had closed Youssef (9) suggested a functional valve w the cervical portion of the fistula but was un to localize such a valve Instead he proposed that there might be sufficient pressure in the isthmic sphincter leading the menstrual blood to the bladder This latter explanation was however regarded as un likely by Tancer (8) who proved that amenorrhea and cyclic hematuria persisted without urinary incon tinence even if the uterine fistulous tract was localized below the anatomical functional isthmus

We believe that the explanation might be found in the pressure gradients seen between these two hollow organs Normally the pressure in the filling phase of the bladder in females rarely exceeds 20 cm H_2O (10) When the detrusor muscle contracts the intravesical pressure in females rises to but rarely exceeds 50 cm H_2O Normally the intravesical pressure during void ing in females is between 20 and 50 cm H_2O Intra uterine pressure varies and depends on the phase in the menstrual cycle It is highest during menstruation when pressures between 130 and 160 cm H_2O have been recorded In the intermenstrual phase pressures are substantially lower in the proliferative phase pressures between 35 and 70 cm H_2O have been re corded and in the secretory phase pressures are high er 55 to 100 cm H_2O (1 5) Therefore the pressure in the uterine cavity seems to be higher than the pressure in the bladder except during micturition

When a patient with a vesico-uterine fistula voids there may be a flow of urine from the cervix because of the increased intravesical pressure but this may be difficult for the patient to observe

In this case it was possible to localize the fistulous tract by means of a cystogram as in the case reported by Sammour (7) In his case hystero-salpingography



Photo at operation af pening the bladder The e joining the anterior osterior wall is seen (ar A cannula is introduced fistolous opening

did not show any communication between the uterus and the bladder We did not try to visualize the fistula by hystero salpingography which was done in the case reported by de Carvalho (3) The possibility of visualizing the fistula seems to depend on the pressure applied during the cystogram and/or the hystero salpingography and the phase in the menstrual cycle

The diagnosis is easily established by the history if the examining doctor is familiar with this syndrome The combination of cesarean section amenorrhea and cyclic hematuria in the absence of urinary incontinence is pathognomic for a vesico uterine fistula In order to further delineate the exact localization of the fistula urethro cystoscopy and roentgen ray examinations such as cystography and/or hystero salpingography may give further information

In our case there was also a dense fibrous bridge between the anterior and the posterior wall of the bladder Residual urine amounted to 24 ml and the patient had a urinary tract infection The symptoms of frequency and dysuria can be explained by the infection and the fibrous bridge in the bladder These symptoms disappeared after division of the bridge and treatment of the urinary tract infection The etiology of the bladder lesion was a cesarean section but in this case the bladder was closed in a way that joined the anterior and posterior wall

The management of this type of fistula is very much the same as for other types of urinary fistulae Transabdominal repair opening of the bladder and localization of the opening of the fistula is recommended for those not familiar with vaginal surgery The dissection of the fistulous tract between the ventral surface of the uterus and the bladder is facilitated and more safely performed if ureteral catheters are inserted The uterine and vesical portions of the fistula should be excised and closed and it is adv… interpose a pedicled omental flap and secure it… the suture line

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CASE REPORT

INCORRECT DIAGNOSIS OF PLACENTAL INSUFFICIENCY IN A PATIENT WITH PRE ECLAMPSIA

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act A case of pre eclampsia is described where suspi f placental insufficiency arose due to low estriol levels positive oxytocin challenge test (OCT) The cause er of these findings was later proven to be strictly fe is concluded that low estriol levels and a positive OCT e caused by a decreased placental capacity but specific of placental function as for instance estimations of n plasma and/or a DHAS-test should be used to veri ule out a suspicion of placental insufficiency

ot in cases of placental sulphatase deficiency (7) apacity of the placenta to form hormones seems rallel the placenta s nutritive and respiratory tion This is the basis for using hormone assays management of high risk pregnancies Some in hormones such as HPL are entirely placen origin whereas some steroids in particular l are formed in the placenta from fetal precur 2)

tepartum monitoring of the fetal heart rate pat n response to uterine contractions (OCT) is a widely used test for evaluation of placental function (4) A fetal heart rate pattern with late decelerations is believed to indicate uteroplacental insufficiency (4)

CASE REPORT

A 32 year old woman gravida IV para II was admitted to the hospital in the 37th week of pregnancy due to hypertension and headache The gravidogram (8) was without obvious deviations An ultrasonic measurement of the fetal biparietal diameter was done and found normal (9? mm) Her urinary excretion of estriol however was below normal (6) on 3 consecutive days An antepartum OCT (Fig 1) showed learly defined late decelerations With these facts at hand it was presumed that this pregnancy was complicated by a placental insufficiency and the pregnancy was terminated by a cesarean section The child a boy weighing 3 010 g had a severe malformation of the heart He died at an age of 5 days

A DHAS-test (1) was performed the day before delivery The result which was not available when the decision of premature intervention was made showed that the placenta had an increased capacity (Fig 2) An estimation of HPL in plasma (5) likewise showed a high value (8 8 µg/ml)

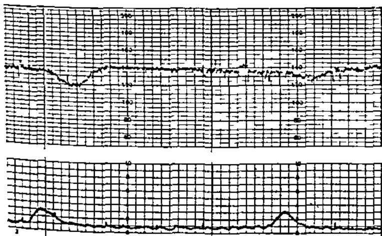


Fig 1 The fetal heart rate pattern in response to uterine contractions

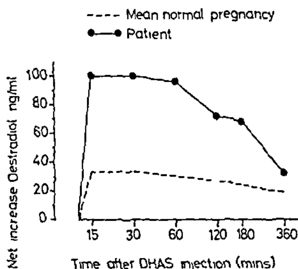


Fig 2 The increase of plasma oestradiol in response to an intravenous injection of 50 mg dehydroepiandrosterone sulphate (DHAS)

DISCUSSION

A reduced blood supply to the placenta a common finding in pre eclampsia (3) may cause a decreased nutritive and respiratory function of the placenta a placental insufficiency A premature induction of delivery may then be indicated in order to avoid fetal starvation or even death A combination of low estriol levels and a positive OCT is most often taken as a sign of placental insufficiency and preterm delivery is recommended regardless of the result of fetal lung maturity tests (4) The present case however shows that a disturbed placental function is not a prerequisite for the occurrence of low estriol levels and a positive OCT Such findings may be caused by a diseased fetus and thus recorded even in pregnancies with a quite normal placental function

If estimations of HPL in plasma and/or the DHAS test had been in clinical use the suspicion of placental insufficiency could have been ruled out in this case

The DHAS-test is probably safer for assessment of placental function (1) than are estimations of HPL in plasma The estimation of HPL is however more simple to perform than is the DHAS test

Since the induction of a premature delivery is indicated in cases with placental insufficiency this diagnosis must be as safe as possible to avoid unnecessary delivery of premature infants Low estriol lev[els] positive OCT are not conclusive for diagnosi[ng pla]cental insufficiency These findings should [pro]cause suspicion of decreased placental fun[ction] suspicion that can be verified or ruled ou[t by] DHAS test or a measurement of HPL in [pl]...

ACKNOWLEDGEMENT

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CASE REPORT

MASSIVE EXTRAPERITONEAL BLEEDING — A RARE COMPLICATION OF AMNIOCENTESIS

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ract Amniocentesis is a widely used procedure infre tly associated with complications A patient in the 16th of pregnancy is described in whom amniocentesis for purpose of genetic counselling was complicated by e extraperitoneal bleeding into the abdominal wall ssitating the surgical evacuation of a large hematoma bleeding most probably resulted from the accidental ture of the right deep epigastric artery

niocentesis is a procedure widely used in the high obstetric patient near term as well as for mid iester artificial abortion and for the purpose of tic counselling in early pregnancy The risk atten t on the procedure is minimal and severe com ations are infrequent (3) The incidental perfora of a relatively large blood vessel of the ab inal wall is very rare and may constitute a lethal er to the parturient if not recognized Such a plication is reported occurring during am entesis performed for genetic counselling pur s

CASE REPORT

a 37 year old gravida II para I was admitted to the aron Hospital for amniocentesis in the 16th week of nancy In view of the fact that sonar B scan examina had located the placenta in the left lower anterior and al wall of the uterus amniocentesis was performed out difficulty through a right lower-quadrant ab inal tap Clear amniotic fluid was obtained and sent to aboratory for genetic studies One hour after the pro re the patient complained of pain and tenderness over ite of the puncture which grew rapidly worse She was r pale and complained of increasing weakness Blood ure was 100/60 but the pulse rate was 105/minute rvation and palpation of the abdominal wall revealed a edly tender bulge in the area of the tap i e the right r quadrant of the abdomen The abdomen was soft ntraperitoneal bleeding was suspected and no ec chymosis of the skin was noted The uterine size cor responded with the dates reported and fetal heart sounds were heard Hemoglobin was found to be 7 5 g per cent (it had been 10 9 g per cent prior to amniocentesis) The clinical picture was one of severe internal bleeding con sidered to be an abdominal wall hematoma resulting from amniocentesis In view of the fact that within hours the swelling extended upwards to the right costal margin and downwards to the symphysis pubis and that the patient s general condition had become worse she was given a transfusion of 3 pints of blood and transferred to the operating room Through a right paramedian incision above the pubis a large hematoma of about 1 500 ml clotted blood was found upon opening the fascia and was evacuated The source of bleeding behind the right rectus muscle was thought to be a perforated right deep inferior epigastric artery The artery was ligated the area was drain ed by a penrose drain and the abdominal wall was closed

The postoperative course was uneventful and the patient was released seven days after the procedure The was delivered spontaneously of a healthy baby boy in the 39th week of pregnancy

COMMENT

During the first half of pregnancy the greatest risk of amniocentesis is the possibility of inducing a traumatic abortion maternal complications are infre quent An abdominal wall hematoma while mention ed as complicating the procedure is a rare occurrence indeed A review of the literature reports only 2 cases of severe hemorrhage among many thousands of am niocenteses performed all over the world (1 2)

The case presented here indicates that ex traperitoneal or subfascial bleeding may be a hazar dous even potentially lethal complication

The artery which was perforated in our case was apparently the right deep inferior epigastric artery which arises from the external iliac artery superior to the inguinal ligament and ascends further finally be

ing located along the abdominis rectus In order to avoid perforating this artery or its accompanying veins the selection of the site where the needle is introduced for the purpose of amniocentesis is very important in the second trimester the site preferred is a midpoint between the uterine fundus and the symphysis pubis as close to the midline on the mother s abdomen as possible and as low as possible

This complication though extremely rare should be borne in mind and evacuation of the hematoma if it continues to increase in size should be done without delay since it may increase the morbidity of the mother even to the point of a severe and possibly fatal outcome

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CASE REPORT

REATMENT OF ADVANCED OVARIAN CANCER WITH FIBRINOLYTIC INHIBITOR (TRANEXAMIC ACID)

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ract A patient with inoperable advanced ovarian r with metastases and ascites who had received several es of radiotherapy and chemotherapy is presented On th admission therapy with the fibrinolytic inhibitor xamic acid was followed by arrest of ascites and tumor th then at exploratory laparotomy examination of r cells revealed encapsulation of fibrinoid substance proliferation of connective tissue The patient still ing tranexamic acid is now free from noteworthy toms

tment of advanced ovarian cancer with ascites is most common major problem of gynecologic gnancy At present three conventional modes of tment are available surgery radiation therapy hemotherapy Regardless of such treatment on liation can be expected and recurrence is often ipt Therefore paracentesis radiotherapy and iotherapy are not always effective in controlling scites in patients with advanced ovarian cancer

the other hand malignant ovarian tumors ss both coagulative and fibrinolytic properties by involving formation of fibrin and conversely val of residual fibrin Consequently high nts of fibrinogen/fibrin degradation products) were demonstrable in the serum as well as the c fluid in patients with such malignant tumors) It was demonstrated experimentally and ally by Astedt (9 10) that tranexamic acid as an itor of plasminogen activation can prevent the lution and removal of residual fibrin around the r and bring about suppression of tumor growth tment with tranexamic acid accordingly gave a able outcome with regression of the clinical toms and arrest of tumor growth for patients advanced ovarian cancer as well as breast r

is paper describes a case of inoperable advanced an cancer with ascites in which adjuvant therapy with the fibrinolytic inhibitor tranexamic acid resulted in a good effect with disappearance of ascites and arrest of tumor growth

CASE REPORT

The patient, aged 60-year-old gravida 3 para 0 was admitted to hospital in April 1977 complaining of persistent abdominal tumors and ascites probably originating from advanced ovarian cancer stage IV It was her sixth admission to the hospital Her present illness had begun with the first admission in 1972 but at that time the patient received linear radiation (5 000 rads) and infusion of colloidal gold (50 mCi) into the peritoneal cavity because of her inoperable state Thereafter temporary remission was obtained, but her clinical symptoms reappeared and further treatment with anticancerous agents such as esquinon (alkylating agent) 5-FU and picibanil (ok-432) in addition to repeated paracentesis was tried

However signs of growth of tumors did not regress and the interval to recurrence gradually shortened. After a two-month interval from her fifth admission in February 1977 her general condition became worse by reason of distended lower abdominal mass increased ascites and nutritional disturbance

The chest film showed no metastatic foci but remarkable adhesion and large bowel mass were revealed by roentgenogram The hydrops and stenosis of the ureter compressed by tumor mass were also demonstrable by pyelogram while dilatation as well as congestion were observed by pelvic angiogram

Coagulative and fibrinolytic studies using blood and ascitic fluid were carried out PTT was shortened and plasma fibrinogen concentration showed approximately 400 mg/dl. Although the plasminogen concentrations in the plasma and ascitic fluid tended to be extremely low a rapid increase of FDP titers in ascitic fluid was observed exceeding 10 μg/ml and then serum FDP concentrations were also significantly higher than those of benign ovarian tumors (Fig 1)

On the other hand inhibitor activity of α1 antitrypsin was slightly higher compared to levels of [illegible] such as α_2-macroglobulin and antithr

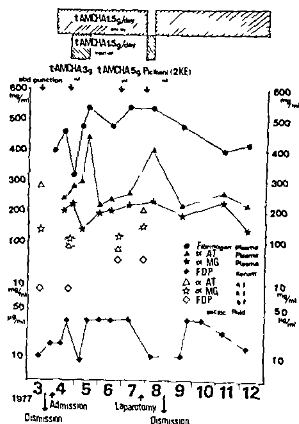


Fig 1 Fibrinogen FDP and some fibrinolytic inhibitor levels in a patient with advanced ovarian cancer during an tifibrinolytic therapy

Thereafter the fibrinolytic inhibitor tranexamic acid [Transamin (t AMCHA) Danchi] was given in a dose of 1 5 – 2 0 g three times a day every day sometimes augmented by infusion of tranexamic acid (3 – 5 g) into the peritoneal cavity or intravenously

After 3 months treatment with tranexamic acid the pro duction of ascitic fluid regressed and finally disappeared Therefore repeated paracentesis was no longer necessary As a result an outline of abdominal tumor masses previ ously obscured by ascites became distinct and an ex ploratory laparotomy was undertaken At laparotomy strong adhesion between a thickened peritoneum with omentum and the thick wall of an encapsulated ovarian tu mor was observed and beneath it large intestinal masses with marked adhesion were also seen The wall of the ovarian tumor was removed and the adhesions of intestinal masses were repaired as far as possible but most of metastases still remained Microscopically the tumor mass was confirmed as being metastases of mucous cystadenocar cinoma of the ovary but in some parts of the specimen the tumor cells were surrounded by proliferating connective tis sue as well as fibrinoid degeneration (Fig 2) Furthermore fibrinolytic activity was found around the tumor tissue us ing a fibrin slide technique The amount of serum FDP gradually decreased

The patient felt well and was dismissed from ho[...] August 1977 She has been free from notewor[...] toms even though treatment with given perorally every day

DISCUSSION

Ovarian cancer is often associated with effu[...] series of 61 patients with stage III ovarian ascites in various degrees was present at dia[...] 82 per cent (2) Combined treatment with sur[...] diotherapy and chemotherapy is effective in [...] ling the ascites and in treatment for ascite[...] centesis should be avoided because of the as[...] loss of an already depleted protein and el[...] store However there is no appropriate tr[...] program for the management of recurrences may often develop at diminishing intervals a[...] initial course of treatment

In general it is considered that the fibr[...] mechanism is depressed in cancer patients [...] quently it is difficult to induce fibrinol[...] with cancer which results in the tumor f[...] ing undigested (7) Furthermore O Mera[...] gested that the deposition of fibrin i[...] tissue is essential for the growth and infiltrat[...] mor cells and the clotting factors in ascitic f[...] found to be higher in the presence of [...] nant tumors (1)

Malignant ovarian tumors on the other h[...] sess coagulative and fibrinolytic properties reflected in the occurrence of FDP in 72 per c[...] the sera of such tumor patients (8) and in high[...] centrations in ascitic fluid (5) We have a[...] data to show that FDP levels in ascitic fluid of[...] ian cancer are extremely high (4) In addition no[...] ovarian cells and benign ovarian tumor cells in c[...] culture showed low FDP levels whereas mali[...] ovarian tumor cells displayed high FDP levels [...] view of these findings Åstedt et al (9 10) prope[...] new treatment for advanced malignant tumors [...] coagulant therapy to prevent fibrin deposition [...] bined with antifibrinolytic therapy to preve[...] tion of fibrin already formed This might in[...] more effectively with tumor growth The[...] reported that adjuvant therapy with hepar[...] tranexamic acid has brought about an inhibit[...] tumor growth in two patients with advance[...] cancer as well as ovarian cancer

Although our patient with inoperable a[...] ovarian cancer and ascites was treated several



Fig 2 Island of tumor cells surrounded by vacuolation and proliferation of connective tissue and fibrinoid degeneration (PAS × 00)

adiotherapy and chemotherapy her clinical oms reappeared at a shorter duration For her recurrence single treatment with tranexamic as given As a result the patient has responded bly to such therapy and has been free from her ent clinical symptoms despite the existence of al tumors

emains however to determine whether these esults can be ascribed solely to the antifibrino- nerapy because the patient has received radio- y and chemotherapy for many years Neverthe is report suggests that antifibrinolytic therapy ranexamic acid has a direct effect on regression ites and arrest of tumor growth in the patient dvanced ovarian cancer as reported by Astedt)

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CLINICAL FETAL MONITORING

The usage and relationship to trends in cesarean delivery and perinatal mortality

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ract During the six years 1970 – 1975 62 266 deliveries rred at Women s Hospital Los Angeles Coun Jniversity of Southern California Medical Center Of patients 18 106 (29 per cent) were monitored with an ence of 18 per cent in 1970 which rose to 35 per cent in The patients were divided into monitored and un tored groups for comparison of cesarean section rates various aspects of perinatal mortality The overall ean section rate was 9 6 per cent with 2 830 cesareans rmed in monitored patients (16 per cent) and 3 124 in unmonitored a 7 per cent incidence including repeat ean The cesarean rate remained remarkably stable the 6-year study period even though the monitoring in ce nearly doubled From 1970 to 1975 the intrapartum rate fell progressively in contrast to the incidence of partum fetal deaths which remained unchanged all 50 per cent survival rate was achieved in the birth nt range of 1 200 grams A particular group of atal patients who apparently benefited from intrapar monitoring were those liveborns with birth weights of grams or less Over the study period the neonatal ality in monitored patients declined whereas mortality neonates which were not monitored during labor re ed high

introduction and rapid acceptance of electronic itoring in obstetrical practice is self evident simplified techniques and improved instrumen n application has been expanded to include partum heart rate testing (2 7 13 16) and the en ement of total intrapartum monitoring in y institutions The question of applicability of in artum monitoring in the high risk patient is m raised and a number of current studies seek to s the impact when monitoring is attempted in all nts (3 14)

though two prospective studies have attempted fine the role of intrapartum monitoring in high pregnancy the benefits and liabilities associated monitoring have not been unequivocally quan d (5 11) Documentation of complications is usually in the form of case reports or retrospective review in which liability is only partially revealed (1 4 6 17) Likewise evidence of benefit is difficult to isolate and measure since concurrent obstetrical procedures are changing as a result of increased interest and an enlightened approach to perinatal care (9 12 15)

At present it is questionable if a prospective con trolled scientific study can be accomplished since it is most difficult to singularly isolate the process of elec tronic monitoring and as the mounting indirect evi dence of benefits raises the ethical questions whether it should be attempted (8) In addition the endpoints judging success such as Apgar scores and acid base are subject to many variable factors The endpoint of intrapartum death although an absolute as shown in this paper is very infrequent thus making it an im practical basis for comparison in a study with limited numbers of patients

In view of the expense need for increased patient sur veillance and the educational demand imposed it is not unreasonable that accumulating evidence regar ding the role of fetal monitoring be examined (8 10) Unfortunately endpoints which seek to measure pregnancy outcome such as Apgar score or neonatal acid base status are not uniformly predictive of long term condition A clearly measurable undisputable endpoint is perinatal death It is recognized that a more ideal critical evaluation would be the assessment of neonatal morbidity CNS sequelae or long term infant follow up This approach unfortunately was not possible within the scope of this study This re port describes the increasing usage of monitoring in a large obstetrical service and explores its possible ef fect on the cesarean section rate The overall trend in perinatal mortality is evaluated and perinatal out come is compared in large monitored and unmoni tored groups

Table I *The yearly incidence of cesarean deliveries is shown with the per cent in parenthesis Cesarean* [illegible] *in monitored patients stabilized at roughly 15 per cent after a significantly higher incidence when mo*[illegible] *was introduced in 1970*

Cesarean section at LAC/USC 1970–1975	1970		1971		1972		1973		1974		1975	
Deliveries	9 775		9 425		9 421		10 434		11 585		[illegible]	
Cesareans	910	(9 3)	822	(8 7)	910	(9 6)	1 068	(10 2)	1 078	(9 3)	1 166	[illegible]
Primary	630	(6 4)	573	(6 1)	617	(6 5)	753	(7 2)	763	(6 7)	[illegible]	[illegible]
Repeat	280	(2 9)	249	(2 6)	293	(3 1)	315	(3 0)	315	(2 7)	[illegible]	[illegible]
Monitored patients	1 798	(18)	2 337	(25)	2 828	(30)	3 329	(32)	3 476	(33)	[illegible]	[illegible]
C/S in monitored patients	354	(20)	360	(15)	465	(16)	539	(16)	533	(14)	[illegible]	[illegible]

MATERIAL AND METHODS

During the six years 1970–1975 62 266 births occurred at Women s Hospital Los Angeles County–University of Southern California Medical Center (LAC/USC) Intrapartum monitoring was instituted on a selective basis in the last three months of 1969 with 10 per cent of patients monitored Due to the large patient volume limitations of available instrumentation and lack of trained personnel an attempt to monitor all patients was not undertaken and is not currently feasible However an increasing attempt was made to monitor all patients with high risk conditions during the years 1973–74 and since then the incidence of monitoring has remained roughly one third of all patients being monitored even though the total number of patients monitored has continued to increase In this selective approach the most common indications for monitoring were poor progress in labor oxytocin administration for augmentation or induction of labor meconium passage hypertensive disorders of pregnancy and abnormal fetal heart tones by auscultation Other common indications included breech presentation maternal medical disorders such as diabetes mellitus and obstetrical complications such as abruptio placenta

The monitored group was thus generally composed [illegible] tients with high risk conditions while the un[illegible] group consisted of patients considered to be [illegible] However it is clear that an absolute definition and [illegible] cation of these groups is not possible since monitoring have been contraindicated in some high risk patie[illegible] their risk condition went unrecognized Conversely patients in the monitored group were no doubt [illegible] with minimal risk indications

A patient was placed in the unmonitored group [illegible] 20 consecutive minutes of interpretable fetal hea[illegible] (FHR) was obtained in order to eliminate cases wh[illegible]

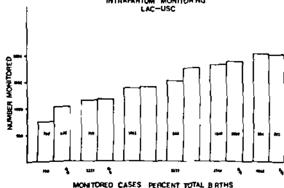
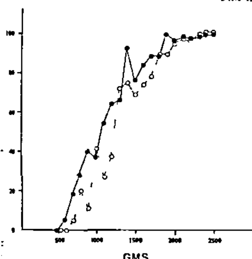


Fig 1 The number of patients monitored increased in each six month interval over six years The relative incidence of monitoring was stable during 1973 through 1975 in spite of a larger total number as a result of more births



Fig 2 Perinatal mortality rates progressively declined during the years 1970–1975 The yearly perinatal mortality defined by the World Health Organization (WHO) [illegible] United States is contrasted The largest reduction in neonatal mortality



3 The neonatal survival in infants weighing ≤ 2 500 g own in a three year comparison An infant has a 50 per chance of survival with a birth weight of 1 200 g

Table II *Overall fetal deaths at LAC/USC 1970–1975 are presented There are approximately four antepartum deaths for each intrapartum death The number in parenthesis is the rate per thousand*

		Fetal deaths 1970–1975
		Number
Total deliveries		62 266
Fetal deaths	(14)	856
Antepartum	(11)	701
Intrapartum	(3)	155
Weight <1 500 g		360
Antepartum		276
Intrapartum		84
Weight 1 500–2 500 g		238
Antepartum		212
Intrapartum		26
Weight >2 500 g		258
Antepartum		213
Intrapartum		45

minimal FHR data which would not likely have served guide in clinical management The FHR UC data was ved by direct methods using a fetal electrode and trans- ical intrauterine catheter in excess of 95 per cent of pa s Indirect monitoring methods were not available in early years of the study period and at present are gener used only when direct methods are contraindicated as in enta previa transverse lie and suspected early labor tal blood sampling was introduced in 1970 and has i extremely useful when abnormal or confusing FHR ings are encountered This supplementary information irrently obtained in about 10 per cent of patients being itored electronically

uring the years studied all neonatal and fetal deaths evaluated Fetal deaths were subdivided into two ips — those occurring antepartum and intrapartum no fetal benefits could be anticipated from intrapar monitoring when death had occurred prior to admis An intrapartum death was therefore arbitrarily defin s a fetal loss occurring after the positive identification etal heart tones or viability on admission to the labor Thus probable labor related deaths such as those seen pruptio placenta prolapsed cord etc were classified as partum deaths whenever the fetal heart activity was ab- t on admission

RESULTS

l Monitoring Usage A total of 18 106 of the 62 births or 29 per cent of all patients were moni d in some way Thus patients with an ante um fetal death were included in this overall total even when only uterine activity was monitored The incidence of monitoring rose from 18 per cent in 1970 to 35 per cent in 1975 The incidence of monitoring plateaued during the final three years although the total number of patients monitored continued to in crease as shown in Fig 1

Cesarean Delivery Of the 62 266 births 5 954 (9 6 per cent) were by cesarean section Of these 4 137 (6 6 per cent) were primary and 1 817 (2 9 per cent) were repeat cesarean sections The yearly incidence is given in Table I and although absolute numbers in creased one will note the relatively stable incidence of this type of delivery over the five years

In general monitoring was used only in patients who had a primary cesarean delivery and not in those undergoing repeat sections A total of 2 830 cesareans were done in the 18 106 monitored patients or an overall incidence of 16 per cent The highest incidence of cesarean section in monitored patients 20 per cent occurred in 1970 with the introduction of this technique Over the subsequent five years the mean incidence was 15 per cent In the unmonitored group of 44 160 patients there were 3 124 cesareans which included 1 817 repeat sections an overall incidence of 7 1 per cent When repeat cesareans were eliminated from consideration in the unmonitored group there were 1 307 sections in 42 343 patients an incidence of 3 1 per cent

Table III *The decreasing trend in fetal deaths is shown for both antepartum and intrapartum groups The de cline in incidence of occurrence is most significant when intrapartum deaths in 1970 are compared to those 1975 The occurrence of antepartum deaths remained relatively unchanged*

	Fetal deaths at LAC/USC						
	1970	1971	1972	1973	1974	1975	Totals
Alive on admission	9 654	9 303	9 318	10 318	11 475	11 497	61 %.
Antepartum fetal deaths	121†	122	103	116	110	1.6†	698
Intrapartum fetal deaths	36	33	34	0	16	16	155
Intrapartum > 1500 g	18	14	17	7	9	6	71

Comparison 1970 vs 1975 † Not significant $p < 0.005$

Perinatal Mortality There were 856 fetal deaths and 735 neonatal deaths during the six year period for an overall perinatal mortality rate of 26/1000 The perinatal mortality rate for the five year period preceding this study 1965 – 1969 was 49/1000 The progressive yearly declines during the six years of this study are shown in Fig 2 with the lowest rate occuring in 1975 One will note that the major reason for the fall in perinatal mortality was the reduction in neonatal mortality

A Fetal Death Of the 856 fetal deaths 701 occurred antepartum and 155 during the intrapartum period as defined previously The occurrence of these deaths by weight group is presented in Table II

The yearly data which document the decreasing incidence of fetal death is given in Table III It is of interest to note that when 1970 is compared with 1975 the overall intrapartum death rate fell from 3 7/1 000 to 1 4/1 000 or 62 per cent whereas the antepartum rate only decreased 13 per cent The significant decrease in occurrence of intrapartum death is even more dramatic when only infants weighing more than 1 500 grams are considered In this group the rate fell from 1 8/1 000 to 0 5/1 000 a 72 per cent decline

B Neonatal Death Neonatal death rates successive year as shown in the lower area of Fig 2 Of the 735 total occurred in 868 infants (1 4 per cent of total births) with birth weights of 1 500 grams or le Newborns that weighed 1 500 grams or less tha counted for 61 per cent of the overal tality

A 50 per cent survival rate was ach weight range of 1 200 – 1 300 grams a 3

Monitored vs Unmonitored Patients sidered in monitored and unmonitored the intrapartum and neonatal death rates The 701 patients with antepartum fetal deaths not considered in either group A pat in the monitored group only when 20 minutes o data was obtained for interpretation and clinical For this comparison a patient was classif unmonitored in cases where only pressure was measured

A Intrapartum Fetal Deaths The comparison of trapartum fetal death in the monitored and un tored groups is shown in Table IV The death ra the monitored group shown in the upper p

Table IV A *Overall monitored versus unmonitored intrapartum fetal deaths at LAC/USC 1970 – 1975 are shown*

	Intrapartum fetal deaths	
	High risk monitored	Low risk unmonitored
Total patients	17 363	44 202
Fetal deaths	24	131
Rate per 1 000	1 4	1 3

Table IV B *Monitored versus unmonitored intrapartum fetal deaths at LAC/USC 1970 – 1975 the corrected comparison in weights over 1*

	Intrapartum fetal deaths	
	High risk monitored	Low risk unmon
Total patients	17 089	43 5 4
Fetal deaths	16	55
Rate per 1 000	0 9	13

le V *Intrapartum deaths in weight > 1500 g (at C/USC 1970–1975) occur less often in monitored ents Patients with severe congenital anomalies birth trauma associated with death are eliminated n both groups*

	Intrapartum fetal deaths	
	High risk monitored	Low risk unmonitored
l patients	17 089	43 524
l deaths	7	36
per 1 000	0 4	0 8

101 p<0 1

significantly lower than the unmonitored group 0 005) with the chi square test However evalua of only these data would be misleading as one her examines these deaths In the unmonitored p 76 of the 131 intrapartum deaths were in very ll fetuses (1 500 grams) whereas only 8 of 24 hs in monitored patients were similarly very ll The unmonitored group thus contained a dis- portionately large number of fetal deaths in very ll fetuses A factor which might explain this find s that monitoring was used infrequently when the s was written off' or felt to be unsalvage particularly during the early years of this y

order to eliminate this factor it was decided to ider fetal deaths in which birth weights exceeded 0 grams There was a total of 71 such deaths with 1 the monitored group and 55 in the unmonitored

le VI *The neonatal mortality rate at LAC/USC)–1975 is compared in monitored and unmonito- groups A similar rate is found in weights over 0 g*

	Neonatal mortality	
	Monitored	Unmonitored
all		
ve births	17 339	44 071
onatal deaths	181	554
te per 1 000	10 4	12 6
500 g		
ve births	17 073	43 469
onatal deaths	90	198
te per 1 000	5 3	4 6

0 05 difference not s gn ficant

Table VII *The neonatal mortality (at LAC/USC 1970–1975) in infants weighing less than 1 500 g is significantly lower in the monitored group This dif ference is most marked in infants weighing 1 000 to 1 500 g*

	Neonatal mortality	
	Monitored	Unmonitored
≤1 500 g		
Live births	266	602
Neonatal deaths	91	356
Rate per 1 000	342	591
1 000–1 500 g**		
Live births	203	363
Neonatal deaths	54	147
Rate per 1 000	266	405
<1 000 grams**		
Live births	63	239
Neonatal deaths	37	209
Rate per 1 000	587	874

$\chi^2=15\ 8$ $p<0\ 005$ $\chi^2=5\ 39$ $p<0\ 025$ $\chi^2=3\ 08$ $p<0\ 1$

group as seen in the lower portion of Table IV A number of these intrapartum losses were associated with recognized severe congenital anomalies or birth trauma in which monitoring per se could not have changed outcome Therefore both groups were simi larly corrected for problems such as anencephaly hydrocephaly with decompression severe shoulder dystocia of more than five minutes and a trapped breech of more than 20 minutes duration

The corrected fetal death rates are presented in Table V and the difference in these rates does not achieve statistical significance but is suggested ($p>0\ 05-0\ 1$)

B Neonatal Deaths The overall neonatal mortality rates for the monitored and unmonitored groups are presented in Table VI Although the overall mortality is strikingly different the death rates are comparable in infants weighing more than 1 500 grams This fin ding could be anticipated since the previously stated factors used as indications for fetal monitoring are known to be associated with an increased mortality Since the mortality rates in infants >1 500 grams are similar the overall differences seen in the total rates must occur in those newborns weighing ≤1 500 grams The comparative data from these neonates is given in Table VII The overall newborn mortality of the monitored group weighing 1 500 grams or less is significantly lower than in the unmonitored group Distribution of neonatal weights was examined and found to be randomly distributed in both groups The

Table VIII *The yearly comparisons of neonatal mortality (at LAC/USC 1970–1975) in monitored and unmonitored neonates ≤1 500 g is given The most dramatic differences are apparent in 1974 and 1975*

	Monitored			Unmonitored		
	Births	Deaths	Mortality %	Births	Deaths	Mortality %
1970	13	5	38 5	127	86	67 7
1971	26	9	34 6	127	80	63 0
1972	34	18	52 9	108	56	51 9
1973	39	20	51 3	86	43	50 0
1974	63	16	25 3	84	52	61 9
1975	91	23	25 2	70	39	55 7
Total	266	91	34 2	602	356	59 1

yearly increases of monitoring usage in small fetuses is apparent in Table VIII The highest mortality rate occurred in 1972 and subsequently has dramatically declined as experience was gained in this type of patient and as more were monitored In contrast mortality in the unmonitored group has remained virtually unchanged over the six years

COMMENT

During the six years evaluated there was a progressive downward trend in perinatal mortality Multiple factors which no doubt contributed to improved outcome were more comprehensive management of complicated medical obstetrical problems improved obstetrical anesthesia vigorous newborn resuscitative procedures and a broadened neonatal intensive care capability

Other factors which also exerted their impact during this time were a liberalized approach to abortion a fall in the incidence of low birth weight births from 9 4 per cent to 7 4 per cent a trend toward cesarean delivery in breech presentation and the introduction of continuous methods of intrapartum monitoring In view of the many factors associated with a declining perinatal mortality it is impossible to state a direct causal role relating only to intrapartum monitoring

The question is often raised does the introduction and usage of clinical monitoring cause the cesarean section rate to rise? Although there was an initial higher incidence of cesarean delivery in monitored patients in 1970 (20 per cent) the cesarean rate over this six year study stayed remarkably stable The finding of an originally higher incidence of cesarean delivery is commonly reported and may be the result of anxiety with overreaction to the new information available However in our experience stability in the rate occurred over the next five years although the incidence of monitoring nearly doubled As expected with selective high risk indications used for monitoring the incidence of cesarean section was higher in monitored patients than in unmonitored patients

The data regarding overall fetal deaths deserve further comment First antepartum deaths were five times more common than those occurring during labor The need for better screening methods to identify such patients and estimate fetal well being is urgent An additional factor possibly reflected in minimal reduction in rate is caused by our patient population which frequently receives little or no prenatal care and because we are a center to which patients with antepartum death are referred. Secondly monitoring will not eliminate intrapartum death although its occurrence will be reduced to an exceedingly low incidence In a critical review of the six monitored deaths there were suggestive abnormal FHR patterns in six instances which if acted upon more rapidly, may have prevented death Thus, in this monitored group of over 18 000 patients, only one unexpected death occurred which was associated with fetal arrhythmia

As one attempts to evaluate the effect of monitoring on outcome an obvious weakness is the comparison of dissimular groups However the monitored group composed of high risk patients should have contributed more heavily to overall mortality. In fact the perinatal mortality in this high risk group was lower than in the unmonitored group In addition to the lower incidence of intrapartum deaths the perinatal patients who as a group benefited most from intrapartum monitoring were those born with birth weights of 1 500 grams or less This finding in particular tends to negate the argument that monitoring merely prevents fetal loss and shifts the

of death into the neonatal period In comparing itored and unmonitored groups it is apparent the presumed normal or unmonitored group ributes significantly to perinatal losses In order nimize mortality and enhance intrapartum care uld seem not unreasonable to extend monitoring ost patients during the labor process

ring the six years of study a different philoso emerged regarding the care of the very small With the availability of expert neonatal in ve care and as a result of accumulating experi s any fetus judged to weigh 1 000 grams or more dered fetal intensive care and would be prompt livered by cesarean section should non-correct fetal distress be encountered The term mptly delivered is chosen since abnormal FHR ngs seem to evolve more rapidly in the small fe reflecting a diminished tolerance This alized approach coupled with more small fetus being monitored has met with gratifying neonatal ts The fetuses weighing between 500–1 000 is are being more frequently monitored even gh operative intervention is ruled out in an at it to correct and minimize possible deleterious ef during labor should the fetus survive The 1 000 is weight selected is arbitrary and may be revised continuing experience and when better determi on of weight is possible

e monitored fetus apparently enjoys an enhanc rvival over his unmonitored counterpart In ad n to mere survival long term benefits may in prevention of brain injury since fetal damage t of death should also be avoidable The desir ty and need for a well-designed perinatal study long term follow up to further evaluate the role inical monitoring is self-evident

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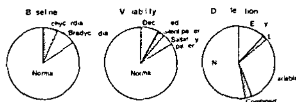


Fig 1 The frequency of the various FHR changes during the first stage of labor in the total material (percentage) n = 2 566

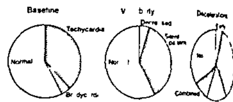


Fig 3 The frequency of the various FHR changes at the deliveries where the newborns had an Apgar score <7 at 5 minutes (percentage) n = 21

per cent VE 1 4 per cent forceps) The uncorrected perinatal mortality was 0 69 per cent No infants died *during delivery*

Table I and Fig 1 show the frequency of various FHR changes in the total material Deviations in basal frequency and variability occurred in about 15 per cent whereas different types of decelerations specially variable or early could be shown in almost 50 per cent of all recordings Tachycardia silent pattern or late decelerations occurred rarely The tracing was completely normal in 40 per cent of all deliveries

Table I and Fig 2 show the frequency of various FHR changes in those newborns that had an Apgar score less than 7 at 1 minute In this group tachycardia during delivery was considerably more common (26 per cent) than in the total material On the other hand the frequency of bradycardia was not appreciable increased In the total material silent pat occurred in only 2 5 per cent but here the proportion had increased to 22 per cent The frequency of late and combined decelerations was also increased to 9 and 11 per cent respectively Only 8 out of 116 newborns in this group had a completely normal FHR recording during the first stage of labor

Table I and Fig 3 list the corresponding figure of newborns with an Apgar score less than 7 at 5 minutes *During 1977 this group included 29 newborns* (0 9 per cent of all births) of whom 21 were rec during the first stage of labor Tachycardia, s *pattern or* late decelerations were the dominant F changes in this group and had already occurred ing the first stage of labor in 18 out of 21 de Bradycardia reduced variability and early decelerations were only exceptionally noted Also the quency of variable decelerations was reduced in group

Fig 4 shows the percentage of newborns Apgar score less than 7 at 1 and 5 minutes at FHR changes About 20 per cent of the that during the first stage of labor had late or combined decelerations had reduced score at 1 minute For silent pattern this was almost doubled (39 per cent) At 5 minutes per cent of all newborns with tachycardia ed decelerations had an Apgar score less than 7 corresponding percentage for newborns with pattern or late decelerations were 12 5 and 16.3 pectively

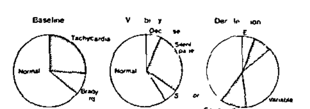


Fig 2 The frequency of the various FHR changes at those deliveries where the newborns had an Apgar score <7 at 1 minute (percentage) n = 116

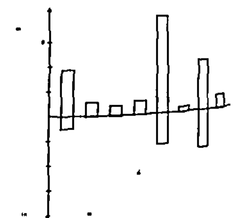
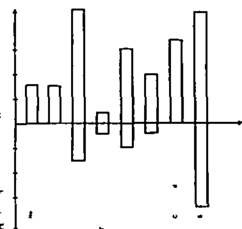


Fig 4 Percentage of newborns with an Apgar score and 5 minutes at various types of FHR changes. F le 19 per cent of all newborns with gar score <7 at 1 minute and 5 per cent at 5 m



Percentage of newborns with an Apgar score <7 at 1 minutes in combinations with tachycardia and other changes

tain combinations of the above mentioned hanges revealed an increased percentage of d Apgar score (Fig 5 and 6)

nbinations of tachycardia silent pattern and ecelerations were found in almost half of the together with reduced Apgar score at 1 minute ame tendency could be found at 5 minutes

DISCUSSION

al maternity clinics report reduced perinatal lity after introducing electronic fetal monitor d pH analysis of the fetal scalp blood (2 7 4) main the proportion of fetal death during ry was considerably reduced Whether morbidi also reduced is so far unclear but recently (15) demonstrated a reduced frequency of injury and also less need for neonatal intensive f newborns monitored with CTG and pH dur livery

present investigation used fetal electronic oring routinely in an unselected delivery al The frequency of various FHR changes is mpared with other published material but this due to other authors not having solely studied hanges during the first stage of labor or mainly ng high risk pregnancies

he 116 newborns found to have an Apgar score an 7 at 1 minute 101 during the first stage of howed one or more of following FHR changes ardia silent pattern late and combined and le decelerations The corresponding figure for newborns with an Apgar score less than 7 at 5 minutes is 18 out of 21

Of the newborns with reduced Apgar score only 8 of 116 at 1 minute and none of 21 at 5 minutes had a normal FHR pattern

This indicates that electronic fetal heart rate moni toring provides possibilities to suspect the diagnosis fetal distress already during the first stage of labor despite the fact that the course of events during the second stage of labor have not been evaluated in this study

However the risk of overdiagnosing fetal distress by CTG is considerable the number of falsely om nious FHR recordings is relatively high (1) This is also noted in this material where the majority of in fants with tachycardia silent pattern late and com bined decelerations had a normal Apgar score (Fig 4) If several of the FHR changes occurred at the same time in the same patient however the proportion of reduced Apgar score considerably increased (Figs 5 and 6)

In order to establish the distress diagnosis several studies have shown the value of pH analysis of fetal scalp blood (10 15) This is illustrated by deliveries in this material where late decelerations appeared Dur ing the majority of these deliveries pH analysis was repeatedly made in fully half of the cases a normal acid base balance could be demonstrated In 60 per cent of these cases of vaginal delivery could be per formed

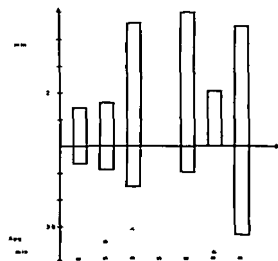


Fig 6 Percentage of newborns with an Apgar score <7 at 1 and 5 minutes in combinations with silent pattern and other FHR changes

In the present study no intrapartal fetal deaths occurred which stress the postulate that these deaths can be reduced with intensive fetal monitoring (9)

The FHR changes in this material have been related to Apgar score as an assessment of the newborns condition The newborns condition could not be related to pH analysis of cord blood as the number of these measurements were too small However the low perinatal mortality and the low frequency of newborns with an Apgar score less than 7 at 1 minutes (4 5 per cent) and 5 minutes (0 8 per cent) may suggest the benefit of intensive fetal monitoring Hochuli *et al* (7) in a review article found a better fetal outcome of newborns who had been monitored during labor and delivery However to which categories of patients fetal monitoring should be restricted if a restriction shall be made seems unsettled (5)

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SELECTIVE VERSUS ROUTINE INTRAPARTUM MONITORING COMPARISON OF EFFECTS ON PERINATAL OUTCOME

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ct This study compares perinatal results of 7 604 de ın two successive years (1976 – 1977) ın which no changes occurred other than a four fold increase ın nic intrapartum monitoring. ıe first year 15 4 per cent of births were monitored ıely In the second year all births were monitored e exception of patients admitted at an advanced stage ır and elective cesarean section The results show no ant improvement either in intrapartum or in early al mortality rates The same results obtained in cesar ction rate and in instrumental deliveries The only e result is a significant reduction of low Apgar scores unselected monitoring group (1977) The low mor is considered to be a result not only of increased mon but also of active management of labor of a short ın of labor and of intensive neonatal care

uality of obstetrical care is currently evaluated rinatal indices i e perinatal mortality and tal morbidity While the contribution of intra n electronic monitoring of labor in reducing tal mortality is well established in high risk de s (9 11 12 13 17) its effect on perinatal mor and neonatal morbidity in low risk deliveries t been clearly defined

orts on intrapartum fetal monitoring may be ied into two groups the first concerning selec onitoring of high risk cases (9 11 12 13 17) e second the routine monitoring of all deliver 5 6 10 14) In the first group the perinatal in of monitored high risk cases cannot be com with those of unmonitored low risk patients e of fundamental differences independent of nitored or unmonitored status In the second of studies perinatal results for a period in more or less universal monitoring was used are red with results recorded in the same institu n premonitoring years The problem in this study is that changes other than monitoring curred during those years which undoubtedly contributed to improved fetal results such as early identification and intensive prenatal care of high risk cases improved management of medical-obstetrical problems higher cesarean section rate better obstet ric anesthesia and improved neonatal care Elimina tion of this bias is a difficult task

The present study deals with perinatal results in two successive years (1976 – 1977) in which no policy changes occurred other than a four fold increase in electronic monitoring of labor

MATERIAL AND METHODS

During the years 1976 – 1977 there were 7 604 deliveries in the Department of Obstetrics A of the Hakirya Materni ty Hospital Tel Aviv The number of newborns weighing 1 000 grams (g) or more was 7 678 In the first year 15 4 per cent of all births were monitored internally The monitored births comprised the high risk (HR) cases as well as the low risk (LR) cases where obstetrical complications developed during labor At the end of 1976 more monitors arrived From the beginning of 1977 all births both HR and LR were monitored internally with the exception of patients admitted at an advanced stage of labor and elective cesarean section The average percentage of monitoring rose to 56 per cent in 1977

With few exceptions all our patients get satisfactory antenatal treatment The obstetrical risk is evaluated within the fifth month of pregnancy and each pregnant woman is scored and classified as HR or LR The HR group gets in tensive antenatal treatment in an HR clinic The LR patients get routine treatment as long as they do not develop any complication If a complication does develop the patient becomes HR and is treated in an HR clinic

Apart from the higher percentage of monitoring in the year 1977 there have been no changes in the treatment of parturients which included changing the position of the pa tient the administration of oxytocin oxygen meperidine and promethazine paracervical pudendal and epidural blocks There is at least one obstetrician in the delivery room 24 hours a day The Chief resident a neonatalogist and an anesthetist are always available This team is well trained in intensive resuscitation of the newborn

Table I *Perinatal death (birthweight ≥ 1 000 g) in selective versus routine intrapartum monitoring*

	Number of deliveries	Number of births	BPMR	ENMR†	No of stillbirths ≥ 1 000 g		
					Ante partum	Intra partum	[illegible]
Selective monitoring 1976	4 065	4 090	12 2	4 7	23	8	31
Routine monitoring 1977	3 539	3 538	11 3	5 4	14	7	

BPMR = Basic perinatal mortality rate (expressed per 1 000 births) † ENMR = Early neonatal mortality rate (expressed per 1 000 [illegible]

Vaginal delivery is permitted in breech presentation if the parturient has already had a vaginal delivery of a full term baby and after performing an abdominal roentgen ray to assess the size of the fetus and to rule out malformations and hyperextension of the head (2) An additional criterion for vaginal delivery in primipara is a normal pelvimetry according to Colcher Sussman (3)

Active management of labor is the method adopted in our department e g early amniotomy and intravenous administration of oxytocin in progressive doses until an optimal uterine activity of 276 Montevideo units in primiparae and 220 in multiparae is reached (15 18) Application of monitors and tracing interpretation is done by the obstetrician as are the assisted births In all births the partogram the method of delivery Apgar at one and five minutes and the monitoring are registered The perinatal results were checked and compared for the years 1976 and 1977 the years of selective and routine monitoring respectively

RESULTS

The basic perinatal mortality rate (BPMR) is defined according to the recommendations of the 7th General Assembly of the International Federation of Gynecology and Obstetrics as the number of deaths occurring before birth or less than 168 hours after birth per thousand births of 1 000 g or more During the selected monitoring period (1976) BPMR was 50/4 [illegible] 12 2/1 000 In the routine monitoring period [illegible] BPMR was 40/3 538 or 11 3/1 000 (Table I [illegible] difference is statistically not significant (p>0 [illegible]

Among the 31 stillbirths recorded in 1976 [illegible] intrapartum deaths (Table I) Three stillborn [illegible] weighed 1 000 – 1 050 g Though death was [illegible] ed in these cases cesarean section was defer[illegible] cause of their prematurity The fourth death [illegible] result of impaction of the shoulder in a fetus [illegible] weighed 3 850 g In the fifth case fetal death [illegible] during the 10 – 15 minutes between admittan[illegible] dures (registration shaving and giving an ene[illegible] transfer to delivery room The sixth death was [illegible] omphalocelic fetus accompanied by hydramnio[illegible] seventh death was the result of neglected [illegible] and misjudgement in the estimation of gesta[illegible] and of the fetal weight which was 1 740 g [illegible] assessed to be about 1 000 g The eigth death [illegible] fetus with placenta velamentosa with rupture[illegible] previa The fetal death was immediate

In the routine monitored group (1977) seve[illegible] of intrapartum death were recorded Fou[illegible] were anencephalic One had hydrocephalus [illegible] weighing 1 090 g had prolapse of cord The [illegible] case was a fetus small for gestational age [illegible] 2 500 g which died a few minutes after adm[illegible]

The early neonatal mortality rate (ENMR) [illegible] ed as the number of early neonatal deaths oc[illegible] less than 168 hours from the time of birth pe[illegible] livebirths of infants weighing 1 000 g or more [illegible] the period of selected intrapartum mo[illegible] the ENMR was 4 6 compared to 5 4 in the [illegible] monitoring period (1977) (Table I) In bo[illegible] the majority of neonatal deaths were d[illegible] malformations and respiratory distress s[illegible] shown in Table II the deaths were quite [illegible] of their monitored or unmonitored status [illegible] the differences in ENMR between the two p[illegible] statistically unsignificant (p>0 05)

Table II *Number of early neonatal deaths*

Diseases	Selective monitoring	Routine monitoring†
Respiratory distress	8	5
Malformations	3	7
Trisomy	3	–
Diaphragmatic hernia	2	–
Sepsis	–	2
Potter s syndrome	–	2
Anencephaly	1	–
Hydrops fetalis	1	–
Others	1	3
Total	19	19

1976 † 1977

o the potential complications of perforation of by internal monitoring not a single case of ation has been documented Special attention so paid to fetal scalp injuries or infections caus- the scalp electrode No significant injuries or ons have been encountered among the new since the introduction in 1974 of the automatic raft scalp electrode in place of the traumatic electrode

cesarean section rate rose from 4 5 per cent in o 4 8 per cent in 1977 The instrumental deliv te rose from 9 2 per cent to 10 5 per cent How neither the change in cesarean section rate nor instrumental delivery rate is statistically signifi p>0 05)

neonatal morbidity directly related to obstet uses has been evaluated by the percentage of nute Apgar scores of 6 or less In the routine ored group the rate was 0 96 per cent (34 cases) i the selectively monitored group 1 66 per cent ises) The difference is statistically significant 01)

DISCUSSION

ell established that the intrapartum monitoring patients has a favorable effect on perinatal This conclusion cannot be extended to oring of LR or normal deliveries Before the ot of universal intrapartum monitoring can be ered proven it is necessary to demonstrate *1*) a cant improvement in perinatal outcome with monitoring *2*) an absence of the same degree provement with the selected monitoring ap- 1 and *3*) a favorable risk benefit ratio in which rovement in perinatal outcome outweighs the nefit ratio associated with an extensive moni ogram None of these important points have learly proved

present study failed to demonstrate any signifi provement as a result of a four fold increase itoring either in intrapartum or in early neo- ortality rates Not a single death can be at d to the monitored or nonmonitored status esults are in contrast with those of Amato (1) und significantly fewer mortalities among red fetuses compared with nonmonitored fe th in HR and in LR deliveries

only positive result is a significant reduction of gar scores in the unselected monitoring peri same result was obtained by Amato (1) We consider the low morbidity in our material to be a result not only of increased monitoring but also of active management of labor of a short duration of labor due to active management and of intensive neonatal care (15 16 18)

It is not our intention here to discredit the concept that routine intrapartum monitoring represents an optimal method of surveillance of labor and access to continuous information We simply wish to point out that the proof of better results in terms of perinatal mortality does not exist Those who advocate the concept have it seems to us an obligation to criticize their program of health care throughout the prenatal to the neonatal care and to acknowledge that the optimal percentage of intrapartum monitoring de pends on multiple variables The appropriate percen tage for each obstetric unit should be chosen accor ding to its health care complex

Apparently we are not alone in our feelings about the effects of staff versus the machine Haverkamp *et al* (7) compared the effectiveness of fetal monitoring with the effectiveness of auscultation of the fetal he art sounds and pointed out that the overall findings make it appear that it may be the staff both nursing and medical and the facilities that are important in achieving an optimal outcome rather than the use of electronic monitoring per se

In the discussion following a presentation on fetal monitoring by Hon Zannini and Quilligan (8) Go- odlin stated that the staff and facilities may be the im portant feature adding It seems most important that this question be resolved before every obstetric unit in the country feels obligated to spend thousands fo dollars for fetal monitors in order to avoid law suits

Since this statement little has been done to resolve the problem We feel that further studies on the risk benefit ratio in selective versus routine monitoring are mandatory

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STUDIES IN NORMAL PREGNANCY

III Fatty acid composition of serum phosphoglycerides and cholesterol esters

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ct Metabolic and hormonal influences on liver lipid
is are reflected in the relative fatty acid composition
m lecithin Thus a sucessive decrease in essential fat
s (EFA) i e n 6 fatty acids during pregnancy would
e an incipient EFA deficiency at the time of delivery
rmore reciprocal changes in linoleic and arachidonic
uring the 1st trimester with an increase in arachidonic
ould suggest an enhancement of the Greenbeg Path
athway II) in lecithin synthesis presumably caused by
n influence During the 2nd and 3rd trimester recip-
hanges in lecithin content of palmitic and stearic
re similar to changes appearing under cholestasis
furthermore suggested that variations in the utiliza
linoleic acid in cholesterol esters (expressed as chol
ester 18 2/lecithin 18 2) might reflect changes in
cholesterol esterification by the enzyme lecithin
erol acyl transferase (LCAT) Then in late pregnan
elation to a subclinical cholestatic liver engagement
activity would increase as judged from this ratio as
the increased linoleic acid in cholesterol esters

lative fatty acid composition of serum lecithin
ot only reflect deficiency states of specific fatty
(the essential fatty acids (EFA) of the n 6
but also hormonal and metabolic influences
hways of lecithin synthesis
major pathway the Kennedy pathway (Path
for lecithin synthesis preferentially results in
pearance of palmitic (1 60) acid in the 1 posi
d linoleic (18 2) or oleic (18 1) acid in the 2 po-
Cholestatic conditions (8) as well as bile acids
(5) appear to enhance this pathway On the
and experiments in the human *in vitro* (19) as
in vivo (2 10 11) reveal that estrogen en
the Greenberg pathway (Pathway II) resulting
ppearance of more lecithin with stearic (18 0)
the 1 position and arachidonic (20 4) acid in
osition Influences on one lecithin synthesis
y appear to cause a reciprocal change in the

The aim of the present investigation was to study metabolic and hormonal influences as they are reflected by the relative fatty acid composition of serum lecithin and cholesterol esters throughout normal pregnancy

MATERIAL AND METHODS

Clinical material Three different series of healthy pregnant women consecutively selected from the Maternal Welfare Unit one series of non pregnant healthy women and one series of postpartum women consecutively selected from the department of Obstetrics and Gynecology were studied

Series I (1st trimester) Twenty pregnant women (mean age 24 4 range 14–40 years) with normal uncomplicated pregnancy were studied at 8–12 weeks (mean 10 6 weeks) of gestation

Series II (2nd trimester) Twenty pregnant women (mean age 26 6 range 20-41 years) with normal uncomplicated pregnancy were studied at 20–24 weeks (mean 21 7 weeks) of gestation

Series III (3rd trimester) Seventeen pregnant women (mean age 25 5 range 18–35 years) with normal uncomplicated pregnancy were studied at 31–37 weeks (mean 33 6 weeks) of gestation

Series IV (post partum) Ten normal post pregnant women (mean age 24 2 range 20–28 years) were studied 2–5 days after an uncomplicated delivery following a normal pregnancy

Series V (non pregnant) Eighteen non pregnant women (mean age 26 2 years range 19–34 years) with regular menstrual cycles and not using oral contraceptives were studied on the 1st or 2nd day of their menstrual bleeding and served as controls

The women in the five series did not differ in mean age had a normal body weight and the pregnant woman a normal weight gain throughout pregnancy Data in Series III IV and V have partially been presented perviously (8 14 15) and are only included for the purpose of comparison *Blood samples* were drawn in the fasting state in the morning centrifuged at 2 500×g for ten minutes The serum was there after immediately recovered frozen and stored at –20 C in glass tubes with teflon screw caps

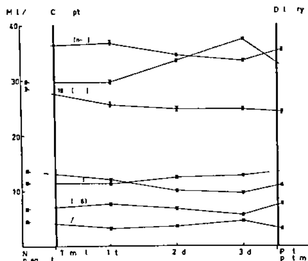


Fig 1 Relative composition of major fatty acids in *serum lecithin* at different stages of normal pregnancy in the non pregnant state and after delivery (post partum) 1st trimester = week 11 2nd trimester = week 22 3rd trimester = week 34 and post partum = 2–5 days after delivery Fatty acid data are given in mole per cent of methyl esters Mean ± SEM

Table II *Mean differences (Δ) in compos... jor fatty acids of serum lecithin at different s... normal pregnancy 1st trimester vs 2nd trime... 1st trimester vs 3rd trimester Lecithin is ... mg/100 ml fatty acid data are given in mole ... of methyl esters*

	1st vs 2nd		1st vs 3rd	
	Δ	P	Δ	
16 0	+ 4 0	**	+ 7.5	
16 1 (n−7)	0	–	− 0 1	
18 0	− 2 1	**	− 2 6	
18 1 (n−9)	+ 1 1	**	+ 1.3	
18 2 (n−6)	− 1 0	–	− 1 0	
20 3 (n−6)	0	–	− 0 1	
20 4 (n−6)	− 0 9		− 2.1	
22 6 (n−3)	+ 0 2	–	− 0 3	
18−22 (n−6)	− 2 4	*	− 3 2	
Lecithin	+49 8	*	+79 0	
16 0/18 0	+ 0 9	**	+ 1 5	
18 2/20 4	+ 0 3	–	+ 1.2	

0 05 level 0 01 level 0 001 level

Preparation of lipids and fatty acid methyl esters Separation of lipids by thin layer chromatography (TLC) on Silica gel with the isolation of lecithin (developing medium chloroform methanol water 65 25 4 by vol) and of cholesterol esters was performed as described elsewhere (13) Preparation of fatty acid methyl esters was performed for lecithin according to the method of Olegård and Svennerholm (13) and for cholesterol esters according to Olegård (12)

Table I *Relative composition of major fatty acids in serum lecithin at different stages of normal pregnancy Lecithin is given in mg/100 ml fatty acid data are given in mole per cent of methyl esters*

	1st[1]		2nd[2]		3rd[3]	
Trimester	Mean	S E	Mean	S E	Mean	S E
16 0	29 85	0 49	33 83	0 49	37 38	0 42
16 1 (n 7)	1 12	0 05	1 11	0 03	1 04	0 04
18 0	12 13	0 27	10 01	0 22	9 54	0 22
18 1 (n 9)	11 33	0 29	12 46	0 27	12 67	0 25
18 2 (n 6)	25 87	0 71	24 90	0 85	24 90	0 44
20 3 (n 6)	2 85	0 11	2 88	0 13	2 76	0 14
20 4 (n 6)	7 86	0 28	6 99	0 29	5 74	0 25
22 6 (n 3)	4 29	0 21	4 48	0 22	4 03	0 24
18 22 (n 6)	36 83	0 65	34 41	0 46	33 66	0 48
Lecithin	182 80	3 94	232 56	6 39	261 65	9 72
16 0/18 0	2 50	0 09	3 47	0 12	3 94	0 08
18 2/20 4	3 39	0 20	3 67	0 19	4 55	0 28

[1] 1st trimester = week 11 of gestation (range 8−12) (n = 20)
[2] 2nd trimester = week 2_ (range 0−24) (n = 20)
[3] 3rd trimester = week 34 (range 31−37) (n = 20)

Gas liquid chromatography (GLC) of methyl este... tracts containing the fatty acid methyl es... evaporated to a final volume of approximately 5 ... was analyzed in a Perkin Elmer Model 30 app... ped with a flame ionization detector on a 200 ... umn (3 mm in inner diameter) packed with 1... diethylene glucol succinate (DEGS) and Chromosorb W DMCS 80−100 mesh N... as carrier gas and the column was operated at 1...

Individual esters were identified by a ... relative retention times of standards (... Inc L 209 and K 108) and phospholipid fat... esters of bull testis Peaks were quantit... the height by the width at half height As shown ... nerholm (18) impurities in solvents interfere wit... mination of 20 5 (n 3) and 2? 3 (n 9) and no ... given for these fatty acids

In addition to the fatty acids presented in th... 15 0 18 3 (n-6) 18 3 (n 3) + 10 1 (n 9) 20 3 (n-9) and 22 5 (n 3) have been identified (18) but n... because their concentrations were generally less t... cent

17 0 (heptadecanoic acid Perkin Elmer) was ... internal standard A known amount of 17 0 was ... the scraped off material of TLC spots before the ... tion procedure

Quantification of serum lecithin Serum lecithin ... tificated from the fatty acid content (obtained by ... ing a nomogram The equation Y = 1 66 ... experimentally determined relationship (8) ... lecithin content as determined by lipid phosphor... amount of lecithin calculated from fatty acid ... For each chromatogram the fatty acid compo... culated as percentage of area (weight per cen...

e III *Relative composition of major fatty acids rum cholesterol esters at different stages of nor pregnancy Fatty acid data are given in mole per of methyl esters fatty acids in mg/100 ml*

	1st[1]		2nd[2]		3rd[3]	
ester	Mean	S E	Mean	S E	Mean	S E
	4 27	0 33	3 09	0 23	3 13	0 32
	12 89	0 24	13 18	0 27	12 16	0 23
(n 7)	2 87	0 19	3 77	0 27	3 7	0 26
	1 35	0 05	1 27	0 07	0 90	0 04
(n−9)	20 34	0 58	23 09	0 69	22 25	0 58
(n−6)	52.23	0 82	50 57	1 04	53.53	0 99
(n−6)	4 30	0 21	3 64	0 18	2 75	0 18
(n−3)	0 31	0 03	0 24	0 01	0 17	0 8
(n−6)	56 06	0 79	53 66	1 00	55 58	0 93
acids	58 15	2 51	73 11	3 48	90 16	3 59
0	9 78	0 36	10 87	0 61	13 57	0 62
20 4	12 85	0 80	14 48	0 76	20 8	1 6

trimester = week 11 of gestation (range 8 − 12) (n = 20)
trimester = week 22 (range 20 − 24) (n = 20)
trimester = week 34 (range 31 − 37) (n = 20)

l esters To obtain the mole per cent distribution conveniently used in metabolic discussions the area each peak in the chromatogram was estimated and d by the corresponding molecular weight for each fat l methyl ester This is described in detail elsewhere (8) *tical methods* Conventional methods were used for ation of means standard deviations and standard er f means Student s t test was used to study differences en different groups and the dependent t test was used analyzing differences between means within groups testing correlation coefficients between different les due consideration was taken to the fact that some m have a functional relationship (i e serum cholester its components) Values of p≤0 05 were considered ically significant (4)

RESULTS

lative fatty acid composition of serum lecithin in st trimester (Table I Fig 1) During the 1st ter (week 11) (as compared to non pregnant serum lecithin contained less stearic (18 0) 001) and linoleic (18 2) (p<0 05) acids while idonic (20 4) acid increased (p<0 05) The ratio en stearic and linoleic acid decreased (p<0 01) *lative fatty acid composition of serum lecithin 2nd and 3rd trimesters* (Table I and II Fig 1) g the 2nd (week 22) and 3rd (week 34) trimes s compared to the 1st serum lecithin fatty acid osition revealed certain characteristic changes tic (16 0) and stearic (18 0) acids were inversely ed as 16 0 increased (p<0 001) and 18 0 de creased (p<0 001) Similarly oleic (18 1) acid increas ed (p<0 01) and sum of n 6 fatty acids showed a de crease with minimum values at week 34 (p<0 001) The ratio 18 2/20 4 increased in the 2nd and 3rd tri mesters as compared to the 1st Arachidonic (20 4) acid decreased in the 2nd (p<0 05) and 3rd (p<0 001) trimester

III Relative fatty acid composition of serum choles terol esters in the 1st and 2nd trimester (Tables III and IV) In the 1st trimester (week 11) arachidonic (20 4) acid ((p<0 05) was more frequently utilized in the esterification of cholesterol while in the 2nd tri mester (week 22) monoenoic acids i e 16 1 (p< 0 01) and oleic (18 1) acid (p<0 01) were relatively more important

IV Relative fatty acid composition of serum choles terol esters in the 3rd trimester (Table III and IV) In the 3rd trimester (week 34) the composition of serum cholesterol ester fatty acid revealed (as compared to the 2nd trimester) an increased amount of linoleic (18 2) acid (p<0 05) The relative proportion of palmitic (16 0) to stearic (18 0) acids in cholesterol es ters was lower in the 3rd as compared to the 2nd tri mester (p<0 01) and (p<0 001) respectively The ratio in cholesterol esters of 18 2/20 4 increased in the 3rd trimester (p<0 001) as did the ratio of choles terol ester 18 2/lecithin 18 2

Table IV *Mean differences (Δ) in composition of major fatty acids of serum cholesterol esters at dif ferent stages of normal pregnancy 1st trimester vs 2nd trimester and 1st trimester vs 3rd trimester Fat ty acid data are given in mole per cent of methyl esters fatty acids in mg/100 ml*

	1st vs 2nd		1st vs 3rd	
	Δ	P	Δ	P
14 0	−1 2		+0 1	–
16 0	+0 3	–	−1 0	
16 1 (n−7)	+0 9		−0 1	–
18 0	−0 1	–	−0 4	
18 1 (n−9)	+2 8		−0 8	–
18 2 (n−6)	−1 7	–	+3 0	*
20 4 (n−6)	−0 7		−0 9	
22 6 (n−3)	−0 1		−0 1	
18−22 (n−6)	−2 4	–	+1 9	–
Fatty acids	+15 0		+17 1	
16 0/18 0	+1 1	–	+2 7	
18 2/20 4	+1 6	–	+6 3	

0 05 level 0 01 level 0 001 level

DISCUSSION

In normal pregnancy there was no apparent reduction in essential fatty acids (EFA) (*Fig 1*) *during the 1st* trimester but during the 2nd and *3rd trimester* there was a successive decrease in all *fatty acids of the n 6 series* i e essential fatty acids This might indicate an incipient EFA deficien y towards the end of *normal* pregnancy Concomitant with the reduction *in EFA* there was an increase in mono enoic acids of the n 9 series in line with earlier experience in EFA deficiency (1 6 *15*)

Furthermore during the 1st trimester the relative *fatty* acid composition of serum lecithin revealed reciprocal changes *in linoleic* and arachidonic *acids* with a reduced ratio in 18 2/20 4 An *increase in* arachidonic acids in early pregnancy was *previously* described by Karkut *et al* (9) We have found an increased relative content of arachidonic acid in *serum lecithin* after the administration of a natural estrogen e g *17 β* estradiol to oophorectomized *women (17)* We interpret the present data as the expression of an *increased* lecithin synthesis by Pathway II due to estrogen influence Such an interpretation would be *in* line with the present knowledge of the hormonal conditions in pregnancy i e *an increased* estriol excretion (7) and estradiol blood level (20)

In mid and late pregnancy i e in the *2nd* and most pronounced in the 3rd *trimester* reciprocal changes in palmitic and *stearic acids* with an increased ratio in 16 0/18 0 *and increased oleic* acid would indicate an enhanced lecithin synthesis by Pathway I A characteristic feature in cholestasis of *pregnancy* is the metabolic influence on *lecithin* synthesis by Pathway I (8) It *is therefore* tentatively concluded that during the 3rd *trimester* an enhanced Pathway I would even in normal pregnancy be an *evidence* for subclinical cholestatic changes in the *liver*

Soon after delivery a *reduction* in this cholestatic influence on liver lecithin *synthesis* is suggested by a decrease in palmitic acid content ($p < 0\ 001$) as well as an increase in stearic ($p < 0\ 001$) *and arachidonic* acids ($p < 0\ 001$) as well as an *increase* in stearic ($p < 0\ 001$) and arachidonic acids ($p < 0\ 001$) in serum lecithin (Fig 1)

During the *3rd trimester* a high utilization of linoleic acid in cholesterol esterification *was shown* This was apparent from the ratio between CE 18 2/Lec 18 2 ($p < 0\ 05$) i e *linoleic acid* content of cholesterol esters and *lecithin* as well as the increased linoleic acid *content* ($p < 0\ 05$) in cholesterol esters In view of the fact that linoleic acid is the *preferable* substrate in cholesterol esterification by the enzyme lecithin [illegible] esterol acyl transferase (LCAT) (16) it is tempting to suggest that during the 3rd trimester an increase [illegible] ratio CE 18 2/Lec 18 2 might be an expression of [illegible] creased LCAT *activity* This would also suggest [illegible] the moderate cholestasis *during la e* pregnancy [illegible] enhance LCAT activity possibly through an increas- ed *enzyme protein* synthesis in the liver as [illegible] *suggested in other* forms of mild cholestasis [illegible]

ACKNOWLEDGEMENTS

Mrs Margareta Medberg is acknowledged for tech[illegible] *sis an e* and Miss Annika Höfde for typing the manu[illegible] This *project* was supported by grants from the S[illegible] Medical Research Council (19C 2100)

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A PROTOCOL DESIGN FOR STUDYING ALTERATIONS OF PHARMACOKINETIC PARAMETERS DUE TO PREGNANCY

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ract A study protocol is described by means of which
il and pertinent information on possible alterations of
macokinetic parameters due to pregnancy can be in
gated Whenever any drug is prescribed to a pregnant
an for medical reasons pharmacokinetic data for that
can be obtained by determination of drug levels in
plasma or serum or other possible tissues The same
should later be obtained for an identical dose of the
drug given to the same woman after pregnancy By
paring pharmacokinetic parameters in the same woman
ig pregnancy and after — when she serves as her own
regnant control — clinically and statistically signifi
differences may be discovered with a comparatively
l patient material As in each case the drug that is
ed is prescribed for medical reasons this protocol in
s no *undue risks for the pregnant woman or the fetus*

macokinetic studies of drugs are usually carried n men rarely in women and very rarely in preg women Due to physiological alterations in y organ systems during pregnancy the pharma etics of most drugs is likely to change This ge may be of such magnitude that an adjustment osage or route of administration might be re d Various reasons why pharmacokinetic param may be altered during pregnancy as well as the for further knowledge concerning such changes been discussed by Ledger (1)

onsidering that treatment with various drugs dur regnancy occurs quite frequently it is surprising so little is known about possible differences in rption distribution and elimination of such s in pregnant as compared to nonpregnant wom The reasons for this is probably that studies of behavior in pregnant women often involve ethic oblems Animal studies will not provide perti data due to differences between species in duration of pregnancy in anatomy in histology and in physiology

The protocol described below was used in an investigation of the pharmacokinetics of ampicillin in pregnant women (2) However the design of the study can easily be applied to other drugs prescribed to pregnant women This study design provides sufficient data to calculate several pharmacokinetic parameters

MATERIAL AND METHODS

In this particular study on ampicillin pregnant women with urinary tract infections served as test subjects All patients were otherwise healthy as judged by their histories physical examinations and routine laboratory tests performed on blood and urine All patients volunteered for the study *which was approved by the Human Experimentation Com* mittee of the Karolinska Institute

The sequence of the study is shown in Fig 1 Each pregnant woman was prescribed 10 days of treatment with oral ampicillin 0 5 g q i d However the first dose of 0 5 g (Dose A) was given intravenously (i v) and comprised the first out of a total of four test doses (i e doses after which concentrations in plasma and urine were followed) The second test dose of 0 5 g (Dose B) was given orally not less than one week (washout period) after completion of therapy

After delivery when the normal menstrual cycle had been reestablished and breast feeding had ceased the third test dose of ampicillin 0 5 g (Dose C) was given as a single i v injection The fourth test dose (Dose D) was given as a single oral dose of 0 5 g not less than one week after Dose C In this way each woman served as her own nonpregnant control

Blood was sampled and urine was collected for determination of ampicillin levels The sampling schedule is shown in Fig 2

Prior to administration of Doses B and D the patients had been fasting for at least 8 hours Food and liquids were allowed 3 hours after dose administration None of the patients were taking any other medication at the time of test doses

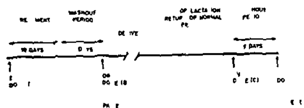


Fig 1 Sequence of test doses of ampicillin in relation to treatment delivery and breast feeding

The weight and gestational length of each patient were registered Urine volumes were measured Drug levels in plasma and urine were assayed according to routine methods

The resulting values of ampicillin in plasma for each patient and dose were plotted against time on arithmetic as well as on semilog scale and provided a plasma concentration versus time curve The arithmetic curve was used to calculate the area under the curve (AUC) which gave a rough measurement of the total amount of absorbed circulating and unexcreted drug and served as a basis for determination of the bioavailability of ampicillin The semilog curve of plasma concentration versus time following i v administration to each patient was used for calculations of plasma half life ($T\ 1/2$) apparent volume of distribution (V_D) and of plasma clearance (Cl_P) of ampicillin

Renal plasma clearance (Cl_R) of ampicillin was calculated for each patient and dose based on mean plasma levels during each urine collection period and the amount of ampicillin recovered in urine during the same time

Statistical analysis was performed with Student s t test for paired observations when these appeared to be normally ributed For clearly skewed observations statistical lysis was performed by sign test for paired observations

DISCUSSION

Previous studies on serum levels of various drugs in pregnant women have usually been carried out simply as dose response studies where the response i e the serum levels resulting from a certain dose of a drug has been measured

However it is a well known fact that pharmacokinetic parameters may vary vastly between individuals Therfore serum levels or other pharmacokinetic data obtained for pregnant women would have to be strikingly different from such data found in a different population to be of statistical significance or the patient sampling would have to be very large

In the above described protocol each woman who has been given a test dose of any drug when pregnant returns after pregnancy to be given additional test doses thereby serving as her own nonpregnan trol This design allows statistical analysis to b on paired observations Thus a comparatively patient sampling is required to detect alter pharmacokinetic parameters due to pregnancy vided test conditions are the same through study

Several pharmacokinetic parameters can be ated if either the i v or the oral route of adm tion is used but by using both routes addi can be obtained By employ i above values can be obtained for peak levels, V_D $T\ 1/2$ bioavailability Cl_R and Cl_P wh include metabolism The dose per kg body weig be calculated

Any drug given sporadically or continuously any length of time to pregnant women can be according to this protocol provided the seque the test dose in the course of treatment is the during and after pregnancy i e single dose pared to single dose and morning dose is co to morning dose in the case of continuous the

The studying of pharmacokinetics of drugs pregnancy is difficult for ethical reasons but protocol is suggested for use only when thera quired for medical reasons it does not imply due risks to the pregnant woman or to the fe taking of several blood samples as well as the ty of having each patient come back after deliv additional test doses requires the test subject well informed volunteers

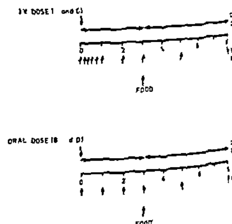


Fig 2 Sampling schedule for blood and urine food intake at i v and oral test doses of amp the 8 h observation period

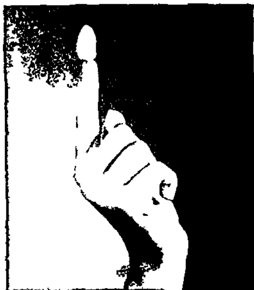
his protocol proved itself to be a simple and use model It can be utilized in full or with modifica for all drugs prescribed during pregnancy the condition being that adequate laboratory iods exist to measure levels in urine plasma or m or other tissues of the drug to be studied If for many and different drugs much valuable in nation about possible changes in pharmacokinetic meters for drugs used during pregnancy could be ined With such increased knowledge the dosages inistered to pregnant women could be better and adequately calculated

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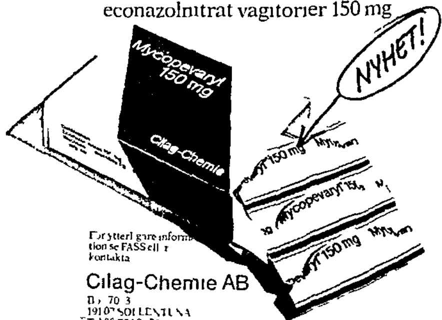


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STUDY OF AMPICILLIN LEVELS IN MATERNAL SERUM UMBILICAL CORD SERUM AND AMNIOTIC FLUID FOLLOWING ADMINISTRATION OF PIVAMPICILLIN

Odd Jordheim and Åse Gerd Hagen

·om the Departments of Obstetrics and Gynecology and Microbiology Drammen Hospital Drammen Norway

act Premature rupture of the membrane is often ed by intrauterine infections Antibiotic prophylaxis ommended but the effect has been debatable rty pregnant women received pivampicillin 350 mg 4 daily The ampicillin levels in amniotic fluid and in the of the fetus and of the mother were determined and l to pivampicillin dose and time after administration he amniotic fluid the average concentration was 3 4 which is considered therapeutic In maternal and erum the ampicillin concentrations were low and took ıost parallel course To obtain the same ratio between illin serum levels and MIC (minimum inhibitory con tion) in the pregnant as in the non pregnant subject a dosage should be used

ıre of the membrane occurs frequently in most nity wards Quite often a long time may pass en the escape and parturition The risk of ding infection is great and the delivery may be licated (11) Prophylactic use of antibiotics is resorted to in this condition The effect of such ıent is still a subject for discussion no satisfac nswer has yet been given (3)

e the introduction of ampicillin various s of its concentration in the fetal circulation been carried out showing that both parenteral ral administration produce therapeutic levels in nniotic fluid (3 8 12 13 14)

purpose of the present study was to determine mpicillin levels obtainable in the amniotic fluid the serum of the mother and the fetus in rela o time after administration

ampicillin tablets (Pondocillin[R] LEO) were istered this being the antibiotic most often us our department and a similar trial with this ıad not previously been performed

/

MATERIAL AND METHODS

The material consisted of 30 patients treated prophylactical ly with 1 tablet (350 m) of pivampicillin 4 times daily Samples were drawn from maternal blood umbilical vein and amniotic fluid at parturition The treatment period therefore varied from hours to several days

Seventy four per cent of the patients had premature escape of amniotic fluid the others had planned section In the latter group we had the opportunity of taking samples at a predetermined time after administration All planned sec tions were however performed in the morning and we did not want to disturb the patients with drug ingestion during the night In these series no amniocentesis was performed just for this purpose

The ampicillin concentrations in the samples were measured by the disc diffusion method (BIODISK) *ad modum* Jalling (4) We used two standard series per set of samples and two discs per unknown sample The values given represent the average of these

RESULTS

In order to obtain a basis for comparison the pa tients were grouped according to the number of hours after the last dose

Table I The ampicillin level in maternal serum um bilical cord serum and amniotic fluid in relation to the total dose administered and the time since the last dose (1–3 hours)

			Concentration level µg/ml		
Pat no	Total dose given (mg)	Time since last dose	Maternal serum	Cord serum	Amniotic fluid
6	1 400	3 0	0	1 1	1 1
7	2 450	1 0	1 6	2 0	4 8
9	700	2 5	0 9	0 4	0 5
20	1 400	2 5	0 7	0 7	4 0
21	2 450	1 0	3 0	0 9	2 2
27	1 050	2 0	0 4	0	1 8
Mean			1 1	0 9	2 4

Table II The ampicillin level in maternal serum um bilical cord serum and amniotic fluid in relation to the total dose administered and the time since the last dose (3 hours)

			Concentration level µg/ml		
Pat no	Total dose given (mg)	Time since last dose	Maternal serum	Cord serum	Amniotic fluid
11	1 050	3		0 2	3 2
12	1 050	3	0 4	0 5	2 3
13	1 400	3	0 8	0 7	5 6
14	1 400	3	1 1	1 2	4 5
15	1 750	3	1 2	1 4	5 5
16	1 750	3	2 7	1	6 4
30	1 400	3	0 7	0 7	3 1
Mean			1 0	0 8	4 4

The concentrations in maternal serum shown in Table I are lower than expected with an average of 1 0 µg/ml The specimens were taken shortly after ad ministration of the drug

The patients in Table II were given 350 mg 3–4 times the preceding day and 350 mg in the morning 3 hours before planned section The values in the am niotic fluid are high with an average of 3 4 µg/ml The serum levels of mother and fetus are low

The results in Table III vary more Three single values in amniotic fluids are below 1 µg/ml The delivery took place after a long interval without medication

As shown in Table IV there is mostly no easureable concentration in maternal serum 9–11

Table III The ampicillin level in maternal serum um bilical cord serum and amniotic fluid in relation to the total dose administered and the time since the last dose (4–4½ hours)

			Concentration level µg/ml		
Pat no	Total dose given (mg)	Time since last dose	Maternal serum	Cord serum	Amniotic fluid
5	1 050	4	0 3	6 4	6 4
8	2 100	4½	0 4	1 3	3
17	1 050	4½	0	0 5	0 8
18	1 050	4	1 8	0 8	2 3
19	350	4	1 5	0 9	1 1
22	700	4½	1	0 8	0 5
28	700	4	0 0	1 5	2 6
29	1 050	4	1 2	1 5	5 4
34	700	4½	2 3	0 6	0 6
Mean			0 9	1 6	2 5

Table IV The ampicillin level in maternal ser[illegible] bilical cord serum and amniotic fluid in relation [illegible] the total dose administered and the time since the [illegible] dose (5–12 hours)

			Concentration level µg		
Pat no	Total dose given (mg)	Time since last dose	Maternal serum	Cord serum	Am[illegible] fluid
10	5 250	11½	0 0	0 8	[illegible]
23	700	12	0 0	0 3	
24	700	11	0 0	1 1	[illegible]
25	700	11	0 0	0 8	5
26	700	11	0 0		4
31	1 050	9	0 7	3 5	[illegible]
32	1 050	5	3 2	1.5	3
33	1 750	7	4	3 1	[illegible]
Mean			1 0	1 4	4

hours after ingestion of pivampicillin but th[illegible] centration in amniotic fluid is still high

The mean values summarized in Table V show the ampicillin concentrations in maternal serum umbilical cords are low and take an almost p[illegible] course while the concentrations in amniotic reach higher levels and last longer

The average concentration in the amniotic fl[illegible] all these patients was 3 4 µg/ml with mean varying from 2 4 to 4 2 µg/ml in the four These values are assessed as being therapeutic highest value was 8 6 µg/ml Levels of 4–5 µ[illegible] were found after 11 hours

DISCUSSION AND CONCLUSIONS

It is important to note that peak concentrations [illegible] reached in the amniotic fluid considerably la[illegible] in maternal serum This might be due to the fa[illegible] the greater part of the ampicillin in amniotic [illegible]

Table V Mean ampicillin levels in ma[illegible] umbilical cord serum and amniotic fluid in [illegible] tients after orally administered pivampicillin [illegible]

		Concentration level µg [illegible]		
	Time since last dose	Maternal serum	Cord serum	Am[illegible] fl[illegible]
Tabl I	1–3 hours	1 1	0 9	[illegible]
Tabl II	3 hours	1 2	1 0	[illegible]
Tabl III	4–4½ hours	0 9	1 6	[illegible]
Tabl IV	5–12 hours	1 0	1 4	[illegible]
Mean		1 1	1.2	[illegible]

inates from the fetus s urinary secretion Normal mpicillin reaches a high concentration in the e

contrast when the fetus is dead the ampicillin es of amniotic fluid are low as shown by Bray has been assumed that the reason is cessation function

investigators have paid attention to the wal of amniotic fluid Plentl showed that half the iotic fluid was renewed within 95 minutes (10) seems to indicate that ampicillin is transferred to amniotic fluid from the maternal circulation and urinary excretion of the fetus makes only a small ribution This study neither verifies nor weakens theories

ie ampicillin levels measured in the amniotic s indicate that prophylactic treatment with n in a dosage of 350 mg 4 times daily is uate

e concentrations in maternal serum are low com with the usual distribution curve These values spond well to the low ampicillin concentrations d in pregnant women in a study performed itly by Philipson (9) there the average concen n was 1 to 2 μg/ml one hour after ingestion of ag of pivampicillin The author concludes that if ame ratio between ampicillin serum level and (minimum inhibitory concentration) is desired pregnant as in the non pregnant subject dou osage should be used

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EMOTIONAL STRESS IN CHILDBIRTH AND ITS MODIFICATION BY VARIATIONS IN OBSTETRIC MANAGEMENT

Epidural analgesia and stress in labor

Peter C Buchan

From the Department of Obstetrics and Gynaecology St James s University Hospital Leeds England

ract Emotional stress before during and after labor measured in 20 primigravidae by serial estimation of na 11 hydroxycorticosteroids and by stress assessment views

ie anticipation of epidural analgesia and internal fetal itoring was a significant source of emotional stress to en awaiting induction of labor despite explanation and apted reassurance

ring labor epidural analgesia reduced stress by abolish ain so eliminating the progressive rise in 11 hydroxy costeroids normally seen throughout labor Epidural esia does not however block the potential for the ad ortical response to stress and the physical work emo- l stress and surgical trauma of delivery stimulate a con able output of 11 hydroxycorticosteroids

MATERIAL AND METHODS

ity primigravidae at between 40 and 42 week s gesta were selected for induction of labor by amniotomy wed by intravenous oxytocin infusion No patient with tension pre-eclampsia adrenal or hepatic disease or a y of psychiatric illness or of corticosteroid therapy in iancy was included

ormed consent was obtained from all subjects follow e antenatal stress assessment interview and after a full nation of the study

means of a semi-structured interview each patient had ional *stress assessed in the antenatal period during* ished first stage of labor and on the second postpar lay All assessments were made by one interviewer who lot involved in the clinical management of the patient interviews the main areas of emotional stress investi related to pain in labor injury to or death of the pa uncertainty about fetal well being and possible injury death of the fetus A score was allocated to each of the ress areas (three fetal and three maternal) Each was l on a 0 – 10 scale giving a score out of sixty points wing the antenatal assessment and without knowledge results the patients were randomly allocated to one of roups and informed of the intended protocol of their

p I Following induction of labor ten patients received ig of pethidine intramuscularly for analgesia as fre ly as it was requested and considered appropriate by ig and medical staff

Group II Ten patients received epidural analgesia through out labor An epidural catheter was inserted and analgesia achieved using 0 25 per cent bupivacaine (without adren aline) the first dose being administered as soon as the pa tient became aware of pain All patients in this group had continuous intrauterine pressure recording and fetal heart rate monitoring throughout labor

Five venous blood samples were taken from each patient the first at 08 00 hours on the day prior to induction the se cond at 08 00 hours on the morning of induction the third when the patient was in established labor with the cervix at least five centimetres dilated the fourth at the diagnosis of full dilatation before the patient was allowed to bear down and the fifth within one hour after delivery Plasma 11 hy droxycorticosteroids were measured by the method of Mat tingley (11)

RESULTS

The stress scores for the antenatal (anticipation stress) intrapartum (experienced stress) and postpar tum (retrospective stress) assessments are shown in Table I

The anticipation stress was the same in both groups and there was no change in the experienced or retro- spective stress compared with the anticipation stress in Group I In Group II the experienced stress was significantly less than the anticipation stress ($p < 0\ 05$) and the retrospective stress was also signifi cantly less than the anticipation stress ($p < 0\ 01$) The level of experienced and retrospective stress in Group II was significantly lower than in Group I ($p < 0\ 01$)

The plasma 11 hydroxycorticosteroid levels in each stage in the two groups and the means and standard deviations are seen in Table II

In Group I there was no difference between the antenatal and preinduction levels the rise from the preinduction to first stage of labor levels was signifi cant ($p < 0\ 001$) as was the rise from the first to the second stage of labor ($p < 0\ 001$) and the rise from the second stage of labor to the postpartum level ($p < 0\ 01$)

Table I A *Stress scores for the antenatal intrapartum and postpartum assessments in Group I patients*

	Patients									
Pethidine analgesia	D W	M V	W L	J M	A M	B C	S M	M M	A.A.	C.A.
Antenatal assessment	48	26	37	52	18	20	54	54	8	[illegible]
Intrapartum assessment	56	36	24	50	8	24	24	40	12	[illegible]
Postpartum assessment	52	32	24	50	6	18	18	28	10	[illegible]

Table I B *Stress scores for antenatal intrapartum and postpartum assessments in Group II patients*

	Patients									
Epidural analgesia	J B	A C	L D	W B	L M	M C	V N	C K	S S	C F
Antenatal assessment	*16*	*36*	*8*	*32*	*16*	*12*	*34*	*39*	*34*	[illegible]
Intrapartum assessment	8	12	6	16	8	4	18	31	17	[illegible]
Postpartum assessment	6	9	4	12	6	4	10	23	18	16

In Group II there was a significant rise from the antenatal to preinduction levels ($p < 0.02$) Although there was a slight fall from the preinduction to first and second stage of labor levels this change was not significant The rise in 11 hydroxycorticosteroids from the second stage to postpartum levels was highly significant ($p < 0.001$)

Comparing Groups I and II there was no significant difference between the antenatal preinduction and postpartum 11 hydroxycorticosteroid levels but both the first and second stage of labor levels in *roup II were significantly lower than in Group I* ($p < 0.001$)

Patients who had an anticipation stress score greater than 30 had a significantly greater rise in their 11 hydroxycorticosteroids from the antenatal preinduction levels compared with those whose anticipation stress score was less than 30 ($p < 0.05$) tients with an experienced stress score greater th had a significantly higher level of 11 hydroxycorticosteroids during the first and second stages of compared with those whose experienced stress was less than 30 ($p < 0.05$)

All patients in the study had vaginal d Two patients in Group I and three in Group II quired assistance with forceps There was no ference in their postnatal 11 hydroxycortico levels compared with patients having spontaneous deliveries

Table II A *Plasma 11 hydroxycorticosteroid levels for Group I patients (nmol/l)*

	Pethidine analgesia				
Patient	Ante natal	Pre induction	First stage	Second stage	Post delivery
D W	1 173	1 501	1 595	2 448	2 095
M V	958	1 049	1 656	2 180	1 995
W L	831	1 018	1 248	1 775	2 360
J M	522	657	795	1 766	2 967
A M	822	1 010	1 813	1 951	2 103
B C	610	792	1 338	2 026	2 305
S M	729	742	1 455	2 255	2 857
M M	555	847	1 181	1 719	2 614
A A	599	712	1 449	2 092	3 331
C A	618	762	1 355	1 855	2 768
Mean	742	909	1 389	2 007	2 540
S D	196	237	269	227	417

Table II B *Plasma 11 hydroxycorticosteroid l for Group II patients (nmol/l)*

	Epidural analgesia				
Patient	Ante natal	Pre induction	First stage	Second stage	Post delivery
J B	847	980	864	938	[illegible]
A C	1 054	1 394	1 005	1 206	[illegible]
L D	604	811	767	767	[illegible]
W B	845	1 024	1 032	1 063	[illegible]
L M	820	1 018	914	1 170	[illegible]
M C	897	1 145	980	980	[illegible]
U N	933	1 339	1 374	1 339	[illegible]
C K	1 195	1 540	1 339	1 071	[illegible]
S S	886	1 063	1 018	[illegible]	[illegible]
C F	723	847	834	811	[illegible]
Mean	880	1 116	1 013	1 015	[illegible]
S D	226	226	190	167	[illegible]

DISCUSSION

rding to Selye (13) stress is a non specific mse of the body to any demand Childbirth s both physical and emotional demands and the mse may be measured by the rise in plasma droxycorticosteroid levels Prior to the onset of most patients experienced some degree of anx often amounting to fear (12) and this was itened prior to the induction of labor This in ed anxiety was reflected both in the stress score in the plasma 11 hydroxycorticosteroid levels

en who had no first hand knowledge of epidural esia or fetal monitoring viewed their intended with some trepidation as shown by the rise in droxycorticosteroid levels between the antenatal reinduction levels in Group II This was despite led explanation and attempted reassurance con ng the procedure involved Although patients in p II had stated that they had had adequate ex ition they nevertheless had greater stress as nced by their increased corticosteroid levels in ipation of labor

th the onset of labor anticipation stress was ented by pain and physical exertion which both ulate adrenocortical activity (3 7) These factors d progressively increasing adrenal stimulation was not a maximal stimulus as shown by the partum rise and by the response of the adrenal to etra-cosactrin given to patients in established by Campbell *et al* (3)

is generally accepted that continuous epidural esia provides the most effective pain relief in (5) It does not directly affect the other stress li of labor but once pain is relieved anxiety and cal exertion are reduced This was clearly seen in p II by the fall in 11 hydroxycorticosteroid from the preinduction level to the first and se stage levels This indicated that pain was the r stress factor in labor and when pain was ed and the fetal condition monitored there was very little stress until the delivery This is in ment with the findings of Lederman *et al* (10) showed a clear relationship between plasma cor and anxiety in labor and Burns (2) who showed plasma cortisol was increased in patients with nged and painful labor

e sharp rise in 11 hydroxycorticosteroid levels wing delivery in Group II confirmed that despite uate analgesia the knowledge that the baby was born the physical exertion of bearing down he surgical trauma of delivery and episiotomy constituted an adequate stimulus to the hypothalamo-pituitary adrenal axis Epidural analgesia did not block the potential for the adrenal stress response it only blocked certain stress stimuli This is of great importance as labor and delivery are times when surgical or haemorrhagic stress are common and the body's protective mechanisms must be able to respond when required

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1982

Date	Place	Name	Office
1980			
October 3–5	New Delhi India	3rd International Seminar on Maternal and Perinatal Mortality Pregnancy Termination and Sterilization	Hon General Secretary The Fed of Obstetric & Gynecological Society of India Purandare Griha 31/c, Dr N A Purandare Marg Bombay 400 007 India
Oct Nov 23–3	San Marino Italy	The Gonadotropins Basic Science and Clinical Aspects in Females	Leslie Nies Symposia Manager Serono Symposia 11 Brooks Drive Braintree MA 02184 USA
November 14–17	Madrid Spain	7 Congrès Européen de Medecine Perinatale	Professor de la Fuente Maternidad de la Ciudad Av Generalissimo 177 Madrid 34
November 18–23	New Orleans LA USA	AAGL Ninth Annual Meeting Clinical Symposium on gynecologic endoscopy	American Association of Gynecologic Laparoscopists 11239 South Lakewood Boulevard Downey California 9[illegible]
November 20–22	Barcelona Spain	Symposiuim International Sobre Monitarizacion Prenatal	Instito Dexeus Srtas M Luis Ana Baldrich c/Paseo de la Bonanova 67 Barcelona 17 Spain
November 22–25	Bombay India	First National Congress on Hormones and Human Reproduction	Mahendra N Parikh Organising Secretary Dr Jhaveri s Hospital, 2[illegible] Lady Hardinge Road Bombay 4[illegible] India
December 1–4	*Kairo* Egypt	*Second Congress of the International Society for the Study of Hypertension in Pregnancy*	*Docent Hjördis Robbe* Dept of Obstet and Gynecol, Karolinska Hospital S-104 01 Stockholm 60 Sweden
December 1–12	Melbourne Australia	Seventh UICC Training Course in Cancer Research	Dr A W Burgess UICC Course, The Walter and Eliza Hall Institute, Royal Melbourne Hosp P O 3050, Victoria Australia

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PIDEMIOLOGICAL ASPECTS OF TOXOPLASMA INFECTIONS AMONG WOMEN IN NORWAY

Babill Stray Pedersen and Anne Marie Lorentzen Styr

From the Department of Obstetrics and Gynecology Rikshospitalet University of Oslo and the Norwegian Defence Microbiological Laboratory Oslo Norway

er to elucidate some of the epidemiological in the acquisition of *Toxoplasma* infections women were requested to answer a series of ir post natal periods Of these women 27 n infected with *T gondii* 84 had old infec ere non infected

given indicated that frequent intake of raw ent travelling abroad especially to countries tion risks were of great significance for the among adults Living in rural districts ap- sent a predisposing factor for the acquisition es Contacts with animals especially cats n to increase the infection risk

l reference to the results obtained a list of sero-negative pregnant women is proposed in nt congenital toxoplasmosis in the Scandina

icy of infections with *Toxoplasma gondii* gnly dependant on the prevailing climatic condi and consequently shows great geographical ations (6) Other factors however which are or less related to the living habits of the popula may also be of significance in the epidemiology uman infections (7) Since the parasite may cause e disease in the fetus (for review see ref 14) it is ially desirable to prevent the infection in the nant woman It was therefore found of interest udy the possible role of some of these factors for acquisition of *Toxoplasma* infections among ien of fertile age in Norway The present study s with the results obtained from a questionnaire ered by a selected group of 196 mothers in the natal period In approximately half of these ien the sero reactions signalled old or recent in ons with *T gondii* the remaining women were negative and served as control subjects The data ined would presumably provide information of rtance for the prevention of congenital tox mosis in our country and perhaps also in the r Scandinavian countries

MATERIAL AND METHODS

Study groups The 196 women under study were all participants in a prospective investigation among 8 043 pregnant women in the Oslo area based on serologic examinations (Dye test and indirect fluorescent antibody test (IgM—IFAT)) on paired antenatal blood samples collected on average in the 13th and the 35th gestational week (16)

Three groups of women were selected

Group I consisted of 85 women who had no detectable *Toxoplasma* antibodies in the two blood samples and were consequently considered to be non infected

Group II comprised 84 women with low *Toxoplasma* antibody titers (10 – 100 IU/ml) and without specific IgM antibodies In these women the acquisition had taken place months or years before the collection of the first antenatal sample and no change in their sero-reactions was observed during the current pregnancy

Group III totalled 27 women who had been infected with *T gondii* during or shortly before the current pregnancy During their gestational period 9 women showed sero-conversion (Dye test negative – 300 IU/ml) 2 showed substantial rise in titer (≥ eightfold rise in titers) 9 had high titers (≥ 300 IU/ml) and 7 women had medium titers (100 – 300 IU/ml) and specific IgM antibodies

The women in Groups I and II were randomly selected but care was taken to make the distribution in the groups as equal as possible with respect to age (mean age = 27 years)

Elements of study Approximately 1 – 6 months after pregnancy the women were asked to complete a simple questionnaire in order to obtain information such as name age address education area (urban suburban rural) and type (apartment house with garden farm) of residence contacts with birds and animals (cats dogs cows sheep etc) eating and cooking habits (consumption of raw and cured meat eggs etc) and visits abroad (name of country) in the past and especially during the current pregnancy

Statistical method The Chi square test with the Yates correction factor was used for the calculation of significance

RESULTS

The information obtained from the questionnaire in the three groups and the statistically significant differences calculated are presented in Table I It will be

Table I *Summary of the individual results*

	Distribution (per cent)			Level of significance		
	I (n = 85) uninfected	II (n = 84) old infection	III (n = 27) new infection	I/II	I/III	II/III
Present situation						
Habitat						
Urban district (apartment)	46	51	67			
Suburban district (house with garden)	52	48	33			
Rural district (farm)	2	1	0			
Contact with animals						
Cats	5	6	4			
Others	6	5	4			
Contact with birds	5	6	7			
Eating habits						
Frequent consumption of raw meat	11	15	33		$p \le 0.01$	[illegible]
Frequent consumption of cured meat	30	33	31			
Frequent consumption of soft boiled eggs	15	25	27			
Travel						
Frequent travel abroad	8	19	31	$0.05 < p \le 0.1$	$0.01 < p \le 0.05$	
Frequent travel to risk countries	5	15	23	$0.05 < p \le 0.1$	$p \le 0.01$	
Childhood						
Habitat						
Urban district (apartment)	45	29	58	$0.05 < p \le 0.1$		$0.01 < p$
Suburban district (house with garden)	35	34	23			
Rural district (farm)	20	37	19	$0.05 < p \le 0.1$		
Contact with animals						
Cats	44	50	48			
Others	40	57	41			
Contact with birds	25	31	26			
Situation during pregnancy						
Travel						
Travel abroad	30	39	52		$0.05 < p \le 0.1$	
Change of residence	29	15	15	$0.05 < p \le 0.1$		

seen that the distribution of the women with respect to location of present residence was practically identical in the different groups The majority lived in urban or suburban districts only three women were living on farms A significantly higher number of the women with old infections (Group II) however had lived in rural districts during childhood compared to the non infected women (Group I) In keeping with this a significantly higher fraction among the non infected and recently infected (Group III) had lived in urban areas as a child compared to the women in Group II

The groups were not found to differ in their replies about animal and bird contact However the recently infected women (Group III) were consuming raw or under cooked meat more frequently than the women in the other groups whereas cured meat or soft boiled eggs appeared to be equally consumed in all three groups

A significantly higher fraction among the infected women (Groups II and III) especially among those recently infected had visited foreign countries in particular those countries where the prevailing risk of *Toxoplasma* infections is considerably higher than in our country During the current pregnancy tr abroad was found to be most frequent among women in Group III whereas change of (i e domestic travel) was found to be more com among the women in Group I

A statistical analysis was performed on some binations of the answers given in order demonstrate any positive or negative correlations shown in Table II travelling abroad was found strongly associated with frequent consumption of meat in both groups of infected women (Groups and III) In contrast these habits were sig less frequent among the women who had grown on farms

DISCUSSION

The upper alimentary tract is believed to represent main portal of entry of *Toxoplasma gondii* and the infection is acquired by contacts with oocyst or by eating the tissue cyst in meat from fected animals (3 8 11) Hutchison and his leagues (9) were able to demonstrate the h

le II *The correlation between some of the answers*

	Total	Groups I	II	III
tive correlation				
equent consumption of raw meat — requent travelling abroad	$p<0\,01$	not significant	$p<0\,01$	$p<0\,01$
itive correlation				
equent consumption of raw meat — ving on farm during childhood	$p<0\,01$	not significant	$0\,05<p\leq0\,01$	not significant
equent travelling abroad — ving on farm during childhood	$p<0\,01$	$0\,05<p\leq0\,1$	not significant	not significant

oocyst in feces from cats orally infected with *T* *ii* Since then special interest has focused on the is one of the main sources of human infections and recent investigations may suggest that this ial is as a permanent carrier of the infection (5)

shown in Table I the present study gave no nce that intimate contact with cats or with other ials actually represented a risk of *Toxoplasma* in ons in the women This finding is in agreement other investigations (1 2 20) However the st shed from cats is remarkably resistant to in 'ices from the environment and can survive in t soil for several months (8 15) The contamina risk might accordingly be expected to be higher ng people handling soil and sand This is sup- ed by the fact that the prevalence of *Toxoplasma* odies in Norway (18) as well as in other coun (13) has been found to be higher among people g in rural as opposed to urban areas Among the en under study a significantly higher fraction of with old infections (Group II) had grown up in areas compared to the women in the other two ps whereas the location of the residence as s appeared to be of no importance in either of roups This again might indicate that people rural districts are more exposed to contamina from infected soil during their childhood than ults

pointed out by several investigators eating raw represents perhaps the main source of human tions (2 12) Meat from domestic animals (e g pigs and cattle) and wild animals (e g hares deers) in Norway has been shown to contain ites (21) However the traditional Norwegian ing habits favor well-done meat which usually been stored frozen both handlings effectively oying the infective tissue cysts (8 22) In recent the consumption of raw or semi raw meat (roast beef beef tartar etc) has become more common As shown in Table I raw meat was consumed significantly more often among the infected women especially among those recently infected compared to the non infected women Moreover raw meat was found to represent the only dietary item which seem ed to entail an increased risk of infection Frequent intake of soft boiled eggs for instance (10) did not correlate with an increased risk of *Toxoplasma* infec tion as also found by Berger and Piekarski (1)

Special attention should be drawn to the fact that travelling abroad was more common among the in fected women in particular among the recently in fected ones ($p<0\,01$) Scandinavians will naturally be exposed to an increased risk of *Toxoplasma* infec tions when visiting South European countries Desmonts and Couvreur (4) have reported that cases of congenital toxoplasmosis in Paris are relatively fre quent among Scandinavian women who marry in France In the prospective serologic study in the Oslo area 13 out of 8 043 women were found to have become infected during pregnancy of whom two women most probably had been contaminated during a visit to Southern Europe (16) Since the frequency of *Toxoplasma* infections in our country may vary from 2 per cent in the North of Norway to about 30 per cent in the South (prevalences at 20 years of age) (18) travelling within our country may presumably also lead to an increased infection risk This could not be confirmed in the present study (Table I)

As shown in Table II international travelling was found to be strongly associated with a frequent intake of raw meat in the groups of infected women (Groups II and III) while these habits were significantly less common among the women who had grown up on farms It is therefore tempting to suggest that socio-economic factors might be of some importance for the epidemiology of *Toxoplasma* infections in our

country The fact that the prevalence of *Toxoplasma* antibodies in the Oslo area has been found to be higher in the wealthier districts of the city (17) constitutes further evidence for this theory It is conceivable that urban citizens having a higher income visit foreign countries more often and are more apt to adopt foreign dishes in their cooking such as raw meat At the same time people who have lived on farms during their childhood may be protected from *Toxoplasma* infections through their living habits as adults

The prevention and control of congenital toxoplasmosis are no doubt accomplished most effectively by means of routine serologic screening of pregnant women since this may lead to rapid treatment of the infected children Nevertheless prophylactic measures may be of great importance in this connection and women should generally be advised to take certain special precautions during the gestational period (7 15 19) Contact with cats should preferably be avoided disposable gloves should be worn when handling cat feces or gardening the hands should be thoroughly washed following contacts with raw meat sand and soil as well as before eating consumption of raw meat should be abandoned As pointed out in the present investigation, women from Norway and other Scandinavian countries should be especially advised to avoid travelling abroad in particular to high risk countries during a pregnancy

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COMBINED ESTROGEN AND PROGESTOGEN FOR THE MENOPAUSE

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act A single blind pilot study using combined estro- nd progestogen therapy was undertaken in 25 patients period of six months in an attempt to evaluate symp- ic control the acceptability or otherwise of bleeding ns and the effect on endometrial pathology

o different progestogens were employed i e norges nd norethisterone acetate and each was given in com on with estradiol valerate in a cyclical and a continu egime

nptomatic control was good in all groups but there mild recrudescence of some symptoms during the free interval in the cyclical groups Regular bleeding was reported in almost all cases receiv clical therapy and unscheduled bleeding was noted in on continuous regimes

dometrial hyperplasia did not occur following treat in any of the groups and there was a return to the nor istology in two patients in whom hyperplasia existed to treatment These results support the view that endo- al hyperplasia is least likely to occur if progestogens dministered in combination with estrogens

ere were no obvious differences between the effects of wo progestogens

relationship of post menstrual unopposed een therapy and endometrial carcinoma has disputed (4 5 9 10 13) however a dose re association has been demonstrated between this of therapy and endometrial hyperplasia (2 12) ew of the possible use of long term estrogen py to prevent the occurrence of an osteoporotic (1 6 7 8) there has been obvious concern over sks involved

ently data have been published showing that ddition of a progestogen may reduce the in ce of endometrial hyperplasia (2 6 12) par rly in the work by Sturdee *et al* (11) where the nce of hyperplasia was also shown to be related duration of progestogen therapy being 12 per n cy lical unopposed estrogen therapy 8 per n cyclical estrogen therapy with a progestogen during the last 5 days of the treatment cycle and nil when the progestogen was added during the last 10 – 13 days

Preparations are available with a progestogen add ed in the latter half of the cycle but in view of the re ported increased incidence of endometrial carcinoma with the use of sequential oral contraceptives (3) and lack of any such correlation with the combined oral contraceptive it was decided that a pilot study of cy clical combined estrogen and progestogen prepara tions should be carried out in menopausal women Two different progestogens were used in order to study their relative effects

Some of the patients were given continuous thera py to determine whether the effects of these com bined preparations could be extended to provide con tinuous symptomatic relief and freedom from bleed ing without overstimulating the endometrium One group received the estrogen in a twice-daily dose to see if there was better symptom control

MATERIAL AND METHODS

Patients with climacteric symptoms who were at least 6 months post menopausal were randomly allocated to 5 dif ferent treatment regimes with 5 patients in each group The duration of treatment was 6 cycles

A Cyclical estradiol valerate 2 mg + norgestrel 500 µg dai ly 21 days out of 28
B Continuous estradiol valerate 2 mg + norgestrel 500 µg daily
C Continuous estradiol valerate 1 mg b i d + levonorgestrel 250 µg daily
D Cyclical estradiol valerate 2 mg + norethisterone acetate 1 mg daily 21 days out of 28
E Continuous estradiol valerate 2 mg + norethisterone acetate 1 mg daily

A detailed assessment of menopausal symptoms and signs was made before treatment and at 1 3 and 6 months later

The occurrence of withdrawal bleeding and unscheduled bleeding was recorded on diary cards

An out patient curettage was undertaken before and after the 6 months treatment

Table I *Frequency of hot flushes*

		Treatment groups				
	Months	A	B	C	D	E
Hot flushes†	0	5	5	3	2	3
	1	3 (3)	3	3	2 (1)	1
	3	1 (4)	3	3	2 (1)	1
	6	1 (4)	2	1	1 (1)	0

one drop-out two drop outs † no of women with complaints
Numbers in parenthesis are for the 7-day treatment free period

RESULTS

Symptomatology Eight presenting symptoms were of interest the commonest being hot flushes which occurred in 78 per cent of patients followed by depression in 61 per cent night sweating 39 per cent insomnia 35 per cent day sweating 30 per cent dry vagina 26 per cent frequency of micturition 26 per cent and dyspareunia 22 per cent

With the numbers used it is not possible to see if any of the changes over time with treatment are statistically significant However in addition to the reduction in the number of patients having the various symptoms almost all manifested a reduction in the frequency and intensity of symptoms There was a mild clinically observed recrudescence of such symptoms as hot flushes and sweating during the tablet free interval in the cyclical groups An example of these changes can be seen in Table I which shows the number of patients complaining of hot flushes during the study

There were no apparent differences between those given estrogen once as opposed to twice daily nor between the two different progestogen regimes

Bleeding In the cyclically treated groups there was no unscheduled bleeding recorded All of the group A patients reported withdrawal bleeding of slight (n = 4) or normal (n = 1) intensity Of the 27 cycles recorded no blood loss was reported in 2 In group D one patient had no diary card and one was lost to follow up of the 18 cycles recorded no bleeding was n ed in 4 Intensity was recorded as slight or n

In the continuously treated groups B C a termittent spotting was recorded by all but 2 p and was annoying in some One patient r spotting or bleeding on 48 days before withd after 3 months therapy

Endometrium The incidence and histology curettings obtained before and after treatme shown in Table II The main changes shown increase in the number of curettings obtained f per cent before treatment to 68 per cent afte ment and the conversion of a proliferative en rium in the pretreatment sample to secretory e trium after treatment All 7 patients having l liferative endometrium in the pretreatment sam hibited this change Of the 14 patients who h curettings before treatment 7 had no curett review 6 had a normal endometrium (1 prolif 5 secretory) and 1 withdrew

Two patients who had hyperplasia before t were reported to have a normal endometrium months treatment (1 proliferative and 1 sec The pretreatment results were not available commencement of treatment and it was cons reasonable to continue in both cases on the of the presence of a progestogen

There were no obvious differences which c related to the different progestogens

Side Effects One patient in the cyclical group ed the withdrawal bleeding and also compla weight gain In the continuously treated group ting was the commonest volunteered complai patients followed by breast tenderness in 4 gain in 2 and nausea in 1

DISCUSSION

The relationship of the estrogen dose and the ence of a progestogen to the incidence of cyst dular hyperplasia or atypical hyperplasia of the

Table II *Incidence and histology of curettings*

	No of patients having curettage	Curettings obtained	Histology of Endometrium		
			Proliferative	Secretory	Hyperplasia
Before treatment	23	9 (39)	7	–	2
After treatment	22	15 (68)	2	13	–

the figures within parentheses denote per cent

rium was demonstrated by Campbell *et al* (2) y showed an incidence of either form of endomet hyperplasia of 35 per cent in the cyclical unopped high-dose estrogen group with a reduction to per cent in the unopposed low dose estrogen ip a further reduction to 8 per cent in the cyclical -dose estrogen group when a progestogen was ad for 7–10 days and an absence of hyperplasia in cal low dose estrogen group with a progesto- added for a similar period Similar figures by ehead *et al* (12) support this finding

figures quoted earlier by Sturdee *et al* (11) v a similar picture except that in the case of con ous estrogen administered by means of an im t together with 5 days of progestogen orally giv cyclically to induce monthly withdrawal bleeding incidence of hyperplasia was 28 per cent and there also one case of endometrial carcinoma It was intil the duration of progestogen treatment was ded to 10–13 days that the incidence of hyper a fell to zero

this study the failure to demonstrate hyper a in any of the treatment groups and the disappance of hyperplasia in two instances support the ssion that endometrial hyperplasia is less likely associated with a combined estrogen and progen preparation or when the progestogen is pre d for at least 10 days during each cycle

irregular spotting in the continuously treated s renders this particular combination unaccep- clinically and although there is the inconve of regular withdrawal bleeding and a recrudes of symptoms during the tablet free interval in clical groups this would appear to be a neces accompaniment to the safe use of post meno- l hormone therapy

as not yet been ascertained however whether a ned estrogen and progestogen regime has dis dvantages over the sequential preparations with s of a progestogen added or what the optimum chedules are for the various constituents

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1982

Date	Place	Name	Office
1981			
January 26–31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Congr Adm[illegible] 31600 West Chicago Livonia, MI [illegible] USA
March 14–18	Atlanta USA	37th Annual Meeting of the American Fertility Society	The American Fertility Society 1608 13th Avenue South Suite 101 Birmingham Alabama 35205 USA
March 22–26	Berlin West Germany	IIIrd World Congress of Human Reproduction	Dozent L Mettler Frauenklin d. [illegible] Hegewischstr 4 D 2300 Kiel 1
March 27–28	Modena Italy	Symposium on Recent Advances on Pathophysiology of Amniotic Fluid	Scientific Secretariat Dr G C Di [illegible] Istituto di Clinica Ostetrica e Gine- cologica Policlinico Via del Pozzo, 41100 Modena Italy
April 15–17	Gorizia Italy	International Course on Ultrasound in Obstetrics	Filippo Destro Organising Secretary Dept of Obstetrics and Gynecology City Hospital Via Vittorio Veneto [illegible] 34170 Gorizia Italy
May 17–24	Dubrovnik Yugoslavia	4th European Congress on Ultrasonics in Medicine	Professor Asim Kurjak Ljubljanska Stube 41000 Zagreb Yugoslavia
June 9–12	Ostend Belgium	Third International Congress on the Menopause	The International Menopause Society 8 av Don Bosco 1150 Brussels, Be[illegible]
July 1–4	Graz Austria	First International Symposium on Minimal Invasive Cancer (Microcarcinoma)	Secretariat First Symposium on Minimal Invasive Cancer P O Box A–1014 Wien Austria
[illegible]st 24–28	Cambridge England	XIII Acta Endocrinologica Congress	Conference Services Ltd XIII Acta Endocrinologica Congress 3 B [illegible] London SW7 3EY England
Sept Oct	Athens Greece	VIth European Congress on Sterility (ESCO)	Sekretariat Prof Dr K Semm, Frauen- klinik der Universität Kiel Hegewisch- strasse 4 2300 Kiel 1 West Germany
October 25–31	Melbourne *Australia*	Eight Asian Congress of Obstetrics *and Gynecology*	The Organizing Secretary VII *Congress of Obstetrics* and G[illegible] G P O Box 2195T Melbourne 3[illegible] Victoria Australia
1982			
October 17–22	San Fransisco CA USA	Xth World Congress of Gynecology and Obstetrics	Xth World Congress of Gynecology Obstetrics c/o The American Coll[illegible] Obstetricians and Gynecologists, One East Wacker Drive Suite [illegible] Chicago Illinois 60601 USA

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URETHRAL PRESSURE PROFILE IN CONTINENT WOMEN FROM CHILDHOOD TO OLD AGE

T Rud

From the Department of Gynecology The Norwegian Radium Hospital Oslo Norway

ract One hundred and sixty nine urinary continent ıles were examined with simultaneous urethro- ›metry using a dual microtip-catheter It was shown :the maximum urethral pressure and the urethral length ased from infancy to the age of 20 – 25 years eafter the values of these parameters decreased with asing age The bladder pressure remained constant in ifferent age groups

six women aged between 20 and 25 years the neters were mea ured three times during a menstrual No correlation between the fluctuating estrogens gens catecholamines and the urethral pressure or the ral lengths was found

; the last two decades methods have been evolv r determining the urethra s intraluminal :e which is important for urinary continence 7 9) The difference between maximum ıl pressure (MUP) and bladder pressure (BP) is i as closure pressure (CP) When CP is e the individual is continent when it is /e or zero she is incontinent

:e main methods have been employed for the rement of urethral pressure

d filled *baloon catheters (9)*

n-end catheters with constant flow (6 11)

sure transducers placed intraluminally in the hra (3 4 5)

ıough the first two methods have been used ex :ly in the past the equipment is difficult to han nd calibrate Furthermore with open-end ers with constant flow problems arise in ııning the urethral closure pressure which is tant when investigating urinary incontinence 's both methods may give a great variety of ar

microtransducers measure the pressure in a area with high accuracy and reproducibility a dual catheter bladder pressure and urethral pressure can be measured simultanously at rest under stress conditions and during filling of the blad der

Each method has its own normal value With open end catheters the pressure comprises both the intraluminal pressure and the resistance to flow With baloon catheters the measuring section is usually so large that the recording represents the sum of differ ent pressures over a rather long distance This im pedes calculations of the true intraluminal pressure The microtransducer measures just the intraluminal pressure in an extremely small area (approximately 0 75 mm^2) The aim of the present investigation was to determine UP BP and CP — as measured by microtransducer catheters — in healthy women of different ages Furthermore these parameters were studied during the menstrual cycle since it has been claimed that they may fluctuate with estrogen and gestagen levels (10)

MATERIAL AND METHODS

The study comprised 169 healthy women They were divided by age into thirteen groups *6 – 15 years 16 – 20 21 – 25* 26 – 30 31 – 35 36 – 40 41 – 45 46 – 50 51 – 55 56 – 60 61 – 65 66 – 70 and > 71 The youngest girls had been ex amined because of symptoms indicating urinary inconti nence those with no objective signs of incontinence (see below) were included in the present study

The middle age groups consisted mainly of healthy volunteers with no urological symptoms Some women had been admitted to the department because of carcinoma in situ of the cervix Bacterial cultures were negative in all pa tients and cystoscopy was normal The subjects were ex amined with simultaneous urethrocystometry including measurements of the urethral pressure profile according to the Asmussen Ulmsten technique (3 4 5) The bladder was filled at a rate of 25 ml/min with saline heated to body temperature Three consecutive urethral pressure profiles (UPP) were registered at rest at a bladder volume of 200 ml All patients were examined in a semi seated position

Table I *MUP BP and CP in different age groups*

	Age groups												
	6–15	16– 0	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61 65	66 70	[illegible]
Parity	0	0 05	0 04	0 83	1 90	2 11	1 78	1 75	1 81	1 57	1 .8	1.50	[illegible]
MUP	97±6	106±5	110±4	94±5	104±8	81±7	89±5	80±8	84±6	82±7	68±5	66 9	[illegible]
BP	20±2	21±1	20±1	21±1	0±2	16±2	22±1	17±2	.4±1	21±2	22±3	17±1	[illegible]
CP	77±7	85±4	90±4	73±5	84±8	65±7	67±5	63±7	60±6	61±7	46 7	49 9	[illegible]
No	12	18	24	18	11	9	18	12	15	14	7	4	[illegible]

Mean ± SE

Urinary continence was recognized in three ways

1 A negative history of urinary stress incontinence
2 No observed leakage of saline from the outer urethral meatus
3 A positive urethral closure pressure both at rest and at stress

Six nulliparous women mean age 22 years (20–25) were investigated in the same manner at various phases of the menstrual cycle i e early at midcycle and late On these occasions blood samples were taken to determine total estrogens progesteron and the catecholamines dopamine adrenaline and nor adrenaline The techniques for the determinations have been described elsewhere (14).

Calculated parameters The mean of three [illegible] UPPs at a bladder volume of 200 ml was determined [illegible] ed to calculate MUP BP CP FUL and AUL (Fig 1)

Statistics The variations in MUP and BP in different groups were tested for significance by means of [illegible] analysis of variance (F test) (1)

Urethral length (FUL and AUL) was analyzed b[illegible] dent s t test

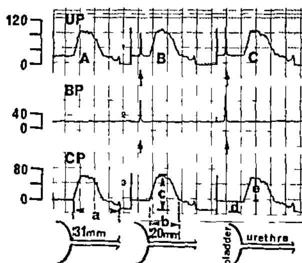


Fig 1 A B and C represent three consecutive urethral pressure profiles in a female The arrows indicate the presence of both transducers in the bladder as the difference between UP and BP at that point is zero

UP = Urethral Pressure
BP = Bladder Pressure
CP = Closure Pressure
a = absolute urethral length
b = functional urethral length
c = maximum urethral pressure
d = bladder pressure
e = closure pressure
Paper speed = 2 5 mm/sec
Catheter withdrawal speed = 2 5 mm/sec
Pressures in cm H_2O

RESULTS

Urethral pressure As seen from Table I and Fig [illegible] MUP increased from a mean of 97 cm H_2O [illegible] 59–115) in the youngest age group to 110 cm (range 76–154) in the age group 21–25 years [illegible] increase was not statistically significant After [illegible]

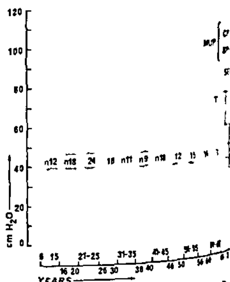


Fig 2 Maximum Urethral Pressure (MUP) [illegible] Pressure (BP) and Closure Pressure (CP) in [illegible] females in different age groups SEM = Standard [illegible] the Mean

I *Urethral lengths in different age groups*

Age groups												
6–15	16– 0	21–25	6–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	≥71
27±2	27±1	30±1	30+2	29±2	27±2	27±1	31±2	28±1	29±1	25±2	.3±2	26±2
31±2	34±1	37±1	37±2	36±2	32±2	35±1	37±2	35±	35±1	32±3	30±2	33±2
12	18	24	18	11	9	18	12	15	14	7	4	7

SE

ears MUP decreased with increasing age For le the difference between the age group 21–25 nd women over 36 years was significant (p < No definite decrease was found in relation to ause

r pressure The bladder pressure did not differ antly between the age groups it remained constant at 20 cm H_2O (at a bladder volume ml)

e pressure Since BP was more or less constant osure pressure showed the same significant se with increasing age as MUP (Table I and

onal urethral length FUL increased from a of 27 mm (range 18–41) in the youngest age to a maximum of 31 mm (range 23–43) in the oup 46–50 years it decreased thereafter to a um of 25 mm (range 18–36) at 70 years and Table II) These differences were significant (p < 0 05) The difference in FUL between women before and after the menopause was significant (p < 0 05)

Absolute urethral length AUL showed the same tendency as FUL and the same statistical significance for shortening after the menopause However in all age groups AUL exceeded FUL by about 5–10 mm

MUP BP CP FUL AUL and catecholamines during the menstrual cycle No definite correlation was found between continence maintaining parameters (MUP BP CP FUL AUL) and estrogen and gestagen levels during the menstrual cycle (Table III)

The catecholamines (dopamine adrenaline and nor adrenaline) showed very small variations during the menstrual cycle and could not be responsible for the variations in MUP during a series of measurements in the individual woman Nor did they influence urethral length (Table III) Only one woman had a detectable level of dopamine

III *Dependence of estrogens gestagens and catecholamines on the urethral pressure profile in six y nulliparae*

Age	Day[1]	MUP[2]	BP[2]	CP[2]	FUL[3]	AUL[3]	Estrogen[4]	Progesterone[4]	Adrenaline[4]	Noradrenaline[4]	Dopamine[4]
22	7	135	24	111	27	36	0 30	1 7	0 1	1 1	–
	14	138	24	114	25	35	0 70	2 0	0 6	1 4	–
	22	141	24	117	27	37	0 61	14 1	0 6	1 0	–
25	9	88	20	68	34	42	0 31	2 2	0 5	1 [illegible]	–
	12	79	16	63	31	44	1 24	1 6	0 4	1 7	–
	23	84	20	64	32	43	0 93	9 9	0 5	1 8	–
20	17	125	28	97	30	42	0 98	2 3	0 5	0 8	–
	24	128	28	100	28	37	0 68	3 0	0 6	1 2	–
	59	116	28	88	27	36	0 90	26 9	0 6	1 0	–
22	6	110	24	86	26	30	0 46	1 5	0 95	1 8	0 16
	12	124	24	100	26	28	0 76	2 0	1 16	1 7	0 6
	22	109	24	85	25	28	1 11	37 3	1 25	1 1	0 4
20	8	134	28	106	29	34	0 18	1 3	1 3	–	
	12	125	24	101	30	34	0 21	2 4	1 2	2 9	–
	22	135	24	111	31	40	0 43	19 5	1 2	2 2	–
21	9	120	20	100	32	36	0 26	1 1	0 7	1 4	–
	13	137	16	121	29	35	0 40	<1 0	0 7	1 1	–
	23	133	28	105	29	34	0 32	<1 0	0 7	1 7	–

cycle [2]cm H_2O [3]mm [4]pmol/L

DISCUSSION

The decrease in urethral pressure with increasing age was demonstrated in 1961 by Enhörning (9) It has been claimed that MUP is highest in childhood (7 12) This study however shows an increase from infancy to adolescence though the results do not provide any explanation for this The increase does not seem to be related to puberty If puberty (with an increasing production of estrogens) and the climacterium (with decreasing estrogen levels) did influence urethral pressure a marked increase would be expected around puberty and a marked decrease after the age of 50 Moreover one would expect a correlation between urethral pressure and estrogen levels during the menstrual cycle The present study showed no such correlation and the decrease in urethral pressure with increasing age was continuous Furthermore the estrogen level in ovulating women is much the same at 21 – 25 and 40 – 45 years of age (2 17)

In an experimental study in the human female we found that blood pressure was responsible for ⅓rd of the maximum urethral pressure (15) The individual tracings revealed a more marked periurethral arterial pulsation in the youngest age groups compared with the older The urethral pressure decrease is therefore more likely to reflect a loss of tonicity in the urethral wall and thicker vessel walls with increasing age thereby diminishing pressure transmission to the urethral lumen

Another study has shown that high doses of estrogens in postmenopausal women increase the aximum urethral pressure only slightly Nor did the gestagen levels seem to influence MUP in these women (16)

In the present investigation the six women examined during the menstrual cycle showed no correlation between estrogen levels and MUP Neither was there any correlation between serum levels of the catecholamines dopamine adrenaline nor adrenaline and MUP

Parity might be one of the causes of the decrease in urethral pressure with increasing age This could theoretically explain the onset of the decrease from 25 years of age However although the material is too small to be divided into parous and non parous the individual pressure tracings showed that MUP fell with increasing age even in the non parous women

The length of the urethra is held to be of great importance for continence (13) It is therefore of interest to find that urethral lengths do shorten after the menopause In another study I found that high dose estrogen treatment elicited a lengthen[illegible] urethra but this lengthening did not [illegible] significantly with improvements in urinary [illegible] continence (16)

At physiological levels however it may be [illegible]cluded that estrogens and gestagens [illegible] catecholamines do not influence MUP or [illegible] length This agrees with Ek *et al* who found [illegible]crease in MUP after therapeutic doses of estrog[illegible] stress incontinent women (8)

According to Edwards and Malvern (7) MU[illegible] healthy women measured by open-end cath[illegible] constant flow can be calculated from the formu[illegible] – age

Pressures measured with the microtip-cath[illegible] however higher as a rule than those obtained [illegible] open end catheters According to this study [illegible]imum urethral pressure — measured by mea[illegible] microtip-catheter with 200 ml saline [illegible] temperature in the bladder and the subject [illegible] seated — in healthy women after the age of 2[illegible] cm H_2O – age ± 20 cm H_2O

ACKNOWLEDGEMENT

The author is indebted to Dr Per K Opsta[illegible] Norwegian Defence Research Establishment, Kjelle[illegible] way for determining the catecholamines in this st[illegible]

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NEUROGENIC BLADDER

teen Walter Knud P Olesen Jørgen Nordlıng Jens T Andersen Hans H Meyhoff and Tage Hald

rom the Departments of Urology and Radiology Herlev Hospital University of Copenhagen Herlev Denmark

ract A survey of the innervation of the bladder and ra is presented Based on the defects of innervation the types of neurogenic bladder disorders are classified escribed The principal diagnostic procedures cysto- and sphincter-electromyography are reviewed in The findings at voiding cysto-urethrography are ed

s important to be able to distinguish between voiding lers of non neurogenic and neurogenic origin

specific treatment of the various types of neurogenic lers of the lower urinary tract is described

ng disorders in the female have traditionally managed by gynecologists In recent years a cooperation has been established between gyne ists urologists and radiologists in the evaluation s group of patients Consultation with a neurol is often indicated to evaluate a possible neuro- l lesion This paper present a short survey of logical bladder disorders that may be encoun in gynecological patients

INNERVATION

in rvation of the lower urinary tract consists of iters and pathways within the central nervous ı and

ipheral neurons

itral nervous system The principal micturition center is localized in the pontine mesencephalic ar formation of the brain stem (6 8) This is responsible for the coordination of bladder ethral function It is influenced by nervous im from three major areas

ical centers ensuring volitional control These have facilitating as well as inhibitory effects brain stem the inhibitory effects prevailing isuring continence

bellar (and possibly other) centers important coordination of the detrusor muscle and the 1 musculature in the pelvic floor and

erent impulses especially proprioceptive initiation and maintenance of micturition

The sacral grey matter contains the motor nerve cells secondary micturition center directly involv ed in the peripheral bladder urethra and pelvic floor innervation The sacral grey matter is controlled by the brain stem micturition center via the reticulo- spinal and pyramidal tracts (6 8) (Fig 1) The sym pathetic outflow to the bladder and urethra is localiz ed in the lower thoracic and upper lumbar spinal segments

2 Peripheral nervous system The peripheral innerva tion is autonomic — both parasympathetic and sym pathetic — as well as somatic (5) (Fig 2)

2a Autonomic innervation The principal efferent in nervation of the detrusor muscle is parasympathetic conducted through the pelvic nerves (nervi erigentes) (11) which are interrupted in synapses in the pelvic ganglia The neuromuscular transmitter in the blad der wall is presumably acetylcholine although other substances may be involved The influence of the sympathetic innervation is still controversial (26) The afferent nerves conducting extero- and propriocep- tive impulses are located within the same nerves with connection to the brain stem micturition center and the central cortex

2b Somatic innervation The striated musculature of the pelvic floor is mainly innervated by the pudendal nerve However recent research seems to indicate that the striated urethral sphincter is not innervated by the pudendal nerve but through the pelvic nerves (9)

Normal micturition During bladder filling the ex teroceptive and proprioceptive input to the central nervous system increases with subsequent activation of the brain stem micturition center and cortex At a certain bladder volume threshold the person will ex perience a desire to void and a micturition reflex is triggered This reflex can be voluntarily suppressed by the cortical centers When micturition is socially convenient the volitional inhibition of the brain stem center is reduced and a coordinated micturition act is elicited via the secondary micturition center in the sacral grey matter

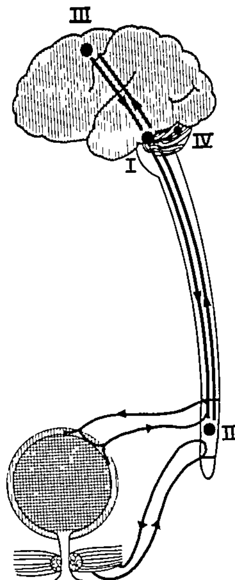


Fig 1 Schematic illustration of the innervation of the lower urinary tract

I Principal micturition center in the brain stem
II Secondary micturition center in the sacral spinal cord
III Cortical centers for volitional control of micturition
IV Cerebellar centers for coordination of bladder and urethral function

CLASSIFICATION

From a clinical point of view neurogenic bladder disorders can be divided into two main groups depending upon whether the neurological lesion is located within (I) or outside (II) the central nervous system (4 17) A third group comprises lesions of the sensory system (III) (Fig 3)

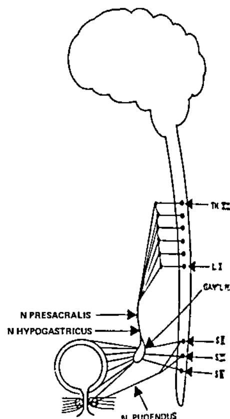


Fig 2 Schematic illustration of the peripheral [illegible] of the lower urinary tract

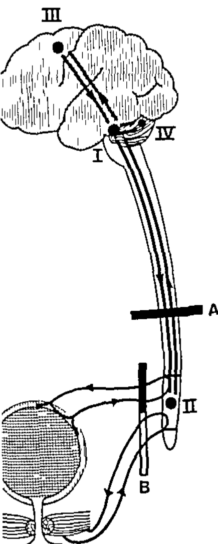
I Upper motor neuron lesion (Supranuclear [illegible] paresis reflex bladder automatic bladder)

This type of neurogenic bladder seen [illegible] above the sacral spinal cord is characterized [illegible] *servation of a micturition reflex* although [illegible] bral control is impaired or completely [illegible] per motor neuron lesions are seen in cerebral insults (24) multiple sclerosis (1) [illegible] spinal cord injury (4) and a variety of other [illegible] affecting the central nervous system

II Lover motor neuron lesion (Infranuclear [illegible] paresis flaccid bladder autonomous bladder)

This type is characterized by *absence of [illegible] tion reflex* Lower motor neuron lesions [illegible] lesions of the cauda equina and conus [illegible] such as protruded lumbar disc (7 10) and [illegible] the peripheral bladder nerves mainly [illegible] jor pelvic surgery (16)

In upper motor neuron lesion as well as [illegible] motor neuron lesion the innervation of the [illegible] floor may be impaired in the upper motor [illegible] sion most frequently leading to pelvic floor [illegible] (detrusor sphincter-dyssynergia) [illegible]



Classification of neurogenic bladder dysfunction ac to location of neurological lesion
er motor neuron lesion
er motor neuron lesion

neuron lesion may be associated with pelvic aralysis However the type of bladder and 1 dysfunction may be dissociated

ripheral neuropathy (Sensory lesion tabetic r)

pheral neuropathy is characterized by *impair f normal bladder sensation initially with pre on of the micturition reflex*

ropathic lesions are typically seen as complica n diseases such as diabetes mellitus (12) per s anemia and tabes dorsalis

DIAGNOSIS

The diagnosis of the neurogenic bladder is based upon a thorough history general physical examina tion clinical neurological examination and cystometry with electromyography (EMG) from the sphincter apparatus

History Two main points should be clarified

1) Vita ante acta Genetic dispositions (e g diabetes) congenital disorders (e g meningomyelocele) trauma (cerebro-spinal pelvic) surgery (major pelvic sur gery neurosurgery) presence of neurological disease (e g multiple sclerosis parkinsonism) gynecological and urological surgery and

2) Actual urological problems Time of onset of void ing symptoms related to age and vita ante acta The micturition pattern should be analyzed with attention to frequency nocturia urgency incontinence (stress/ urge/continuous) difficulty in initiating micturition straining feeling of bladder emptying and pain It is very helpful to have the patient fill in a micturition chart for a period of time (Fig 4) Information should be obtained about present medication with possible effect on bladder function such as anticholinergic drugs Attention should be given to possible rectal and sexual dysfunction

Physical examination includes gynecological exami nation and a gross neurological examination Special attention should be drawn to testing of the sacral reflexes *the anal reflex* where anal sphincter con traction is elicited by inserting a finger in the anal canal *the ano cutaneous reflex* consisting of anal sphincter contraction — elecited by pin pricking the perianal area and *the bulbo-cavernosus reflex* in

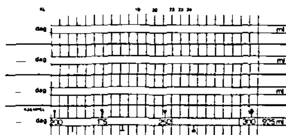


Fig 4 Micturition chart for registration of voiding events during a 3 day period The numbers indicate the voided volumes
= Normal voiding = Dysuria = Severe pain during voiding | = Incontinence episode ⊥ = Change of underwear due to incontinence = Severe incontinence episode = Sleep period



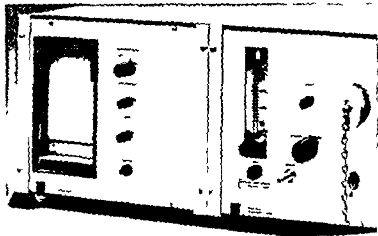


Fig 5 Cystometers
A. Lewis recording cystometer for traditional water cystometry
B DISA type 21G45 cystometer for CO_2-cystometer

hich anal sphincter contraction is triggered by gently squeezing the glans penis/clitoris or pulling on a urethral balloon-catheter Furthermore the sensory innervation of the saddle area should be tested

Cystometry Cystometric investigation can be regarded as the *reflex* hammer used for *testing* the *micturition* reflex The main purpose of *performing* cystometry is testing for detrusor reflex activity This test may *demonstrate presence or absence* of detrusor contractions and the patients ability to actively control these contractions

Other important *information* gained *from* cystometry is the presence or absence of bladder sensation Cystometry can be performed using either water (23) or carbon dioxide (3) as the filling medium (Fig 5)

After emptying the bladder the patient is catheterized transurethrally and the residual urine volume is measured The bladder is filled continuously while intravesical pressure is simultaneously recorded The volume at which first sensation of fullness is experienced is recorded (FS) and the patient is instructed to suppress voiding filling is continued [illegible] the patient feels discomfort The presence of [illegible] contractions with an amplitude exceeding 15 [illegible] during filling is registered as *uninhibited* [illegible] *contractions* (21) If uninhibited detrusor [illegible]tions are not registered during filling the patient [illegible] structed to void in order to se[illegible] if a micturition [illegible] can be demonstrated The patient is then instructed [illegible] inhibit this reflex in order to test the vo[illegible] control

The volitional control is further tested by [illegible] detrusor reflex activating procedures such as [illegible] ing with a full bladder repeated cystometry [illegible] ting standing or walking positions (27)

Testing of the pelvic floor innerva[illegible] and [illegible] ordination between detrusor and pelvic floor [illegible] necessitates the use of simultaneous *sphincter* [illegible]*tromyography* This is most easily perform[illegible] ing a ring electrode mounted on the urethral [illegible] (28) (Fig 6)

A normal cystometry and sphincter [illegible] is shown in Figs 7–8 During bladder fill[illegible] sensation of fullness is usually en[illegible] sensation of fullness is usually [illegible] der volume of *135–215 ml* (34) Normal f[illegible] tion is an important sign of intact [illegible] The maximum cystometric capacity is record[illegible] the patient has a strong *desire* to void [illegible] metry is performed with the patient [illegible] 'holding on' in order to test sphi[illegible] *Upper motor neuron lesion* (Figs [illegible] characterized by uninhibited detrusor [illegible] First sensation — if present at all — is [illegible] enced at a low bladder volume and [illegible]



5 Ring electrode for urethral electromyography (DISA ronics) mounted on a 16 F Foley bag catheter

d by urgency and the onset of uninhibited de or contractions Fig 9 shows the findings in a pa with normal sphincter control whereas Fig 10 s detrusor sphincter dyssynergia characterized sence of volitional control of the sphincter func increasing sphincter contractions during de contraction

ymptoms of upper motor neuron lesion Fre urgency nocturia urge incontinence as seen insonism and cerebral vascular insults In pa with detrusor sphincter dyssynergia further g and impaired bladder emptying are seen or sphincter dyssynergia is seen especially in cord injury but also in patients with e g multi rosis

Lower motor neuron lesion The cystometrogram is characterized by impaired or absent bladder sensation a fairly large bladder capacity and absence of detrusor reflex activity Absence of a detrusor reflex during cystometry may be indicative of a lower motor neuron lesion but the final diagnosis requires testing for denervation supersensitivity (15)

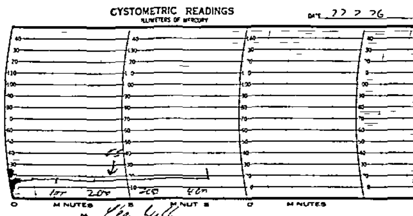
In lower motor neuron lesions after pelvic surgery the pelvic floor innervation is usually intact (Fig 11) whereas lower motor neuron lesions due to lesions of the cauda equina often are associated with pelvic floor paralysis (Fig 12)

Main symptoms of lower motor neuron lesion The symptoms depend upon whether the pelvic floor innervation is intact When it is intact there are often few symptoms over a long period of time When symptoms occur these are often due to a large capacity bladder with high residual urine retention or over flow incontinence When the pelvic floor innervation is damaged severe continuous dribbling incontinence prevails

Peripheral neuropathy This lesion is cystometrically characterized by impaired sensation and a large bladder capacity Detrusor reflex activity is present in the early phases but may be impaired or abolished in the later stages

Main symptoms Few symptoms are present until the patient presents with decompensation of the bladder At this stage urinary retention eventually with over flow incontinence dominates

Radiological examination Radiological examination is not carried out in order to establish the diagnosis neurogenic bladder dysfunction Indications are evaluation of ureteral reflux bladder and urethral diverticula calculi bladder outflow conditions and the relation of the bladder to its supporting structures



Normal water cysto- First sensation at a volume of ml 255 metric bladder capacity 520

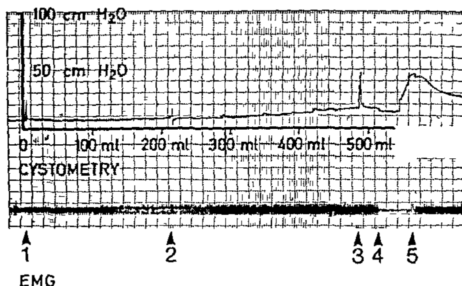


Fig 8 Normal CO_2-[illegible] etry and urethral [illegible] gram
1 Start of bladder [illegible]
2 First sensation [illegible] volume of 210 ml.
3 Cystometric bla[illegible] ity of 490 ml The [illegible] asked to cough [illegible] filling stopped.
4 Patient asked to [illegible] thral electromyogram [illegible] completely and [illegible] onds intravesical rises
5 Patient asked to voiding Urethral gram again shows [illegible] bladder pressure starts [illegible] crease

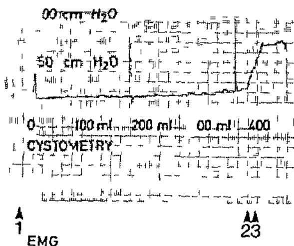


Fig 9 CO_2-cystometry and urethral electromyogram from a patient with multiple sclerosis and upper motor neuron lesion with normal sphincter control
1 Voluntary squeezing before start of bladder filling
2 Uninhibited detrusor contraction starts
3 Patient asked to relax The disappearance of electromyographic activity during the rising phase of the detrusor contraction confirms voluntary control of the sphincter

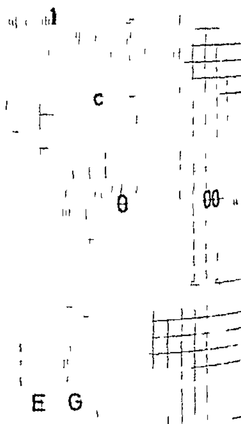
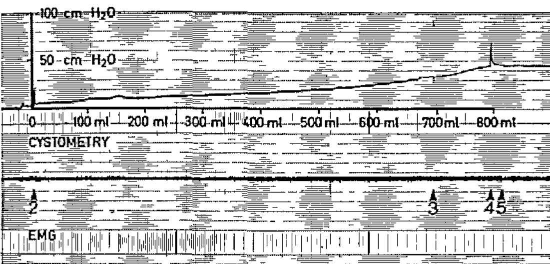


Fig 10 CO_2 cystometry and urethral electro[illegible] a patient with a transverse spinal cord lesion [illegible] per motor neuron lesion with sphincter [illegible] bladder volume of 100 ml an uninhibited detrusor [illegible] is elicited At the same time urethral sphincter [illegible] creases mountly The patient is not able volu[illegible] the urethral sphincter confirming a detrusor [illegible] synergia



11 CO_2-cystometry and urethral electromyogram from ...ent with a lower motor neuron lesion and intact pelvic ... after radical hysterectomy
...oluntarily squeezing before start of bladder filling
...rt of bladder filling
...irst sensation at a bladder volume of 700 ml
4 Cystometric bladder capacity of 800 ml Patient asked to cough and bladder filling stopped
5 Patient asked to void without straining The patient can only shortly relax the sphincter and no detrusor contraction is elicited
A similar cystometrogram is seen in patients with neuropathic lesions

...rtheless neurogenic dysfunctions may be sus...d from voiding cysto-urethrograms (29)

...r *motor neuron lesions* present a rounded blad...nth serrated mucosal pattern as signs of de rusor ... even on the initial film of the supposedly ...ag bladder Cough picture may show active void ...Micturition pictures will show either relaxation ...e urethral sphincter or dilatation of the posterior ...ra due to spastic sphincter detrusor sphincter ...nergia Trabeculation and diverticula are com... (Fig 13)

...*er motor neuron lesions* may be suspected from ...rge bladder volume and/or flaccid appearance ...e bladder at rest Voiding takes place without ... of detrusor function but with abdominal pres... squeezing the bladder against the pelvic floor ... volume urinary retention is common (30) (Fig

...tients with *peripheral neuropathy* may show ... flaccid bladders at rest like the lower motor ...on lesion but voiding may show rounding of the ...ler and serration of bladder mucosa as signs of ...sor function in the early cases Insufficient blad... emptying is the rule (13) (Fig 15)

...ogenic bladder in gynecology The complex pro...s involved in recognition of neurogenic bladder ...nction are of great importance to gynecologists

There are two reasons for this First major pelvic surgery such as radical hysterectomy will often lead to lower motor neuron lesions (16) Secondly among patients referred for urinary incontinence a significant number will have neurogenic bladder dysfunc

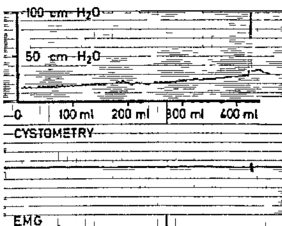


Fig 12 CO_2-cystometry and urethral electromyogram from a patient with traumatic cauda equina lesion and lower motor neuron lesion including a flaccid pelvic floor The patient has no sensation to void and urethral electromyogram is completely silent The filling is stopped at 450 ml due to discomfort



Fog 13 Upper motor neuron lesion Picture at rest Bladder contracted rounded with serration above the trigone as signs of uninhibited detrusor contraction Contrast medium added in the vagina

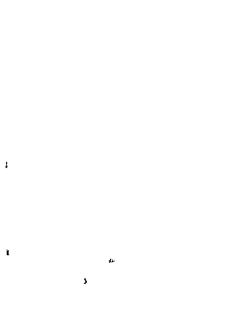


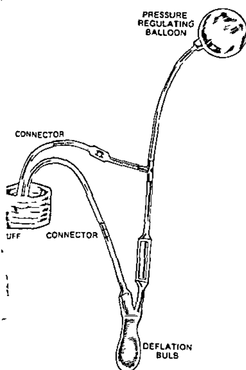
Fig 14 Lower motor neuron lesion Picture at rest La bladder low position

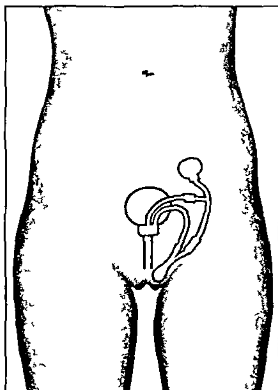
tion It is important to distinguish between the true upper motor neuron lesion and simple urge incontinence The clinical picture may be identical and the diagnoses rest on the urodynamic and neurological evaluation

In a prospective study in Copenhagen county over a two year period 54 out of 369 patients had uninhibited detrusor contractions during cystom[illegible] Of these 54 patients 20 had overt neurological [illegible]ease In 3 of the patients the cystometric uninhibited detrusor contractions was the fi[illegible]tion of multiple sclerosis



Fig 15 Sensory bladder lesion a) Picture at rest large bladder normal position b) During voiding slight rounding and faint serration over the trigone [illegible] detrusor contraction





16 Schematic illustration of the Scott Bradley Timm nence protesis model 742 a) The cuff is implanted at the bladder neck the bulb in the labium majus and pressure regulating balloon is placed intraperitoneally uff keeps the urethra compressed By squeezing the bulb the cuff is emptied into the pressure regulating balloon and the patient is able to void The cuff is refilled automatically after 2 minutes from the pressure regulating balloon b) The artificial Scott Bradley Timm sphincter placed in situ

TREATMENT

r motor neuron lesions are characterized by un ited detrusor contractions This condition is d pharmacologically using parasympatolytic such as emepronium bromide (Cetiprin(R)) (19) methantheline bromide (Banthine(R)) (33) Then al *treatment is* contraindicated or fails resec of the inferior hypogastric plexus a m Ingelman berg (20) sacral nerve blockade or sacral nerve ion (32) come into consideration

ssible bladder outlet obstruction due to pelvic spasticity should only be treated when leading red bladder emptying and recurrent urinary ons The treatment is urethrotomy using the (25) or endoscopic external sphinc my (14) In some patients treatment is ineffec should be supplemented by external collec devices (31) The function of these are however poor in the female therefore some cases are definite candidates for urinary diversion procedures

Lower motor neuron lesions When the pelvic floor innervation is intact the main treatment is by instruction in bladder retraining Because of the few symptoms it is important to diagnose this condition before the patients develop a large capacity bladder with residual urine The treatment consists of instruction in voiding at regular time intervals (every 3 hours during day time) bladder emptying by straining and use of the Crede maneuvre

If the pelvic floor innervation is damaged with subsequent severe incontinence implantation of an artificial urinary sphincter should be considered e g the Scott Bradley Timm sphincter (18)

Peripheral neuropathy is treated in the same way as lower motor neuron lesions If these patients have developed a large bladder capacity and/or residual

urine the treatment should be supplemented by a *parasympathomimetic* drug (e g Carbacholine) (22)

In the treatment of neurogenic bladder disorders urinary diversion or permanent catheter drainage may eventually be inevitable but should only be used as ultimum refugium

The follow up of patients with neurogenic bladder dysfunction is of great importance The main risk in these patients is the development of progressive renal failure Therefore their management should include regular urine cultures and evaluation of renal function

ACKNOWLEDGEMENTS

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ANNOUNCEMENT

The Pan American Congress of Andrology will take place in Mexico City Americana Fiesta Palace Hotel January 26–31 1981

Informations requests for registration and travel information should be directed to

Dr A Negro-Vilar
University of Texas Health Science
Center at Dallas
Southwestern Medical School
Department of Physiology
5323 Harry Hines Boulevard
Dallas Texas 75235
USA

Informations requests for registration and travel information should be directed to

Gerald Bagazinski
Congress Administrator
31600 West Chicago
Livonia Michigan 48150
USA

The Third International Congress on the Menopause [illegible] held in Belgium at the coastal resort of Ostend [illegible] 9–12 1981 just before the holiday season begins.

This Congress will differ from the previous [illegible] Grande Motte 1976 and in Jerusalem 1978) in [illegible] as the aim in the past was to arrive a[illegible] ion this time we shall bravely attempt to con[illegible] troversies It will however take the same [illegible] ones — a number of small workshops rather [illegible] meeting attended by everyone

For further information

The International Menopause Society
8 av Don Bosco
B 1150 Brussels
Belgium
Tel (02) 771 95 98 and (02) 771 96 45

The IIIrd World Congress of Human Reproduction is to be held in West Berlin March 22 26 1981

Main topics

- Central nervous system and regulation of reproduction
- Surgical and morphological aspects of reproduction in men and women
- Gonadotrophins and their target tissue
- Beginning of life *in vivo* and *in vitro*
- Experimental embryology of mammals
- High risk reproductive factors in breast and genital cancer
- Influence of the environment and drugs on reproduction
- Free Communications
- Film Festival

Information.

Congress Secretariat
Priv Doz Dr L Mettler
Frauenklinik der Universität
Hegewischstrasse 4
D-2300 Kiel 1
West Germany

The Eight Asian Congress of Obstetrics and Gynaecology will be held in Melbourne in October 1981

An exciting and varied programme will be presented [illegible] cluding expert plenary speakers from Asia Australia [illegible] other Centres The Congress themes include

- Population Control
- Maternal and Perinatal Mortality
- Trophoblastic Disease
- Gynaecological Malignancy
- Obstetrical and Gynaecological Endocrinology

The official language will be English

Further information may be received from

The Organizing Secretary
VIIIth Asian Congress of
Obstetrics and Gynaecology
G P O Box 2195T
Melbourne 3001
Victoria
Australia

Acta Obstet Gynecol Scand 59 349–353 1980

TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA WITH LOCAL EXCISIONAL BIOPSY AND CRYOSURGERY

Svein Erik Tronstad and Rolf Kirschner

From the Department of Obstetrics and Gynecology Central Hospital Skövde Sweden

ract One hundred and ninety-eight patients with ab-
ıal cytologic smears had extensive diagnostic biopsy of
ortio combined with endocervical curettage Severe
lasia or cancer *in situ* was found in 57 per cent of the
nts During a period of observation of 6–42 months
age 18 months) the cervical intraepithelial neoplasia
) regressed in 54 per cent
yosurgery was used to treat 93 patients with persistent
after biopsy Treatment was successful in almost 70 per
after one single application of cryosurgery The com
tions were negligible Treatment was less successful
increasing histological severity as well as with increas
ge of the patients this applies both to biopsy and
urgery Cryosurgery is significantly less effective when
IN is of both ecto- and endocervical origin
tensive multiple biopsies of the portio in combination
endocervical curettage performed under general
thesia followed by cryosurgery with persistent
ogical abnormalities are indicated as an alternative to
ation especially in younger patients with ectocervical

the introduction of the Papanicolaou smear
t three decades ago the number of patients
ally younger ones with a diagnosis of cervical
epithelial neoplasia (CIN) has steadily increased
20 25) Lately the incidence in Sweden has
7 000–9 000 new cases per year Various
ols for clinical control and treatment of CIN
been advocated from the radical step of im
ate hysterectomy to that of frequent smear con
only For patients with severe dysplasia and car
na *in situ* surgical conization is a very common
od of treatment today (2 9 11 15 17)

nization has disadvantages in the form of im
ate surgical as well as late complications which
be of importance for future fertility and
bearing (5 9 11 13 14) Necessitating
talization it also increases the demands on the
ological department These disadvantages have
o the present indications for conization have
questioned (16)

Colposcopy together with guided excision biopsy and cervical curettage is gaining in popularity (1 7 12) It is a small procedure which can be performed on outpatients and it has been reported to have good results both in diagnosis and treatment (1 2 3 19 25) The last decade has seen the introduction of cryosurgery for the treatment of CIN usually of mild to moderate degree and especially when sited on the ectocervix (3 4 6 10 21 22 23 24)

We decided to investigate

a) The curative effect upon CIN of excisional biopsies of the cervix and

b) Cryosurgery as an alternative method to conization in the treatment of CIN

METHODS

Since 1974 the following regimen for control and treatment of CIN has been used at the Gynecological Department Central Hospital Skövde Sweden (Fig 1)

On finding abnormal smear group III or more (Cytologiskt Laboratorium Malmö Sweden) the patient is referred to histological diagnosis by cervical curettage and extensive multiple biopsies of the portio The operation is done under general anaesthesia on outpatient basis and is guided but not decided by a Schiller test (19) The biopsies are performed with a Hartmann s conchotome (Medicon West Germany) with a diameter of 9 or 11 mm and a depth of excision of 3 mm (Fig 2) Multiple overlapping biopsies extending 3 to 5 mm beyond the margin of the nonstained area together with endocervical curettage give sufficient removal of tissue for a reliable histological examination Electrocautery is used when necessary to control bleeding

In the age groups above 45 years or when abnormal uterine bleeding is present cervical dilatation and curettage of the corpus is added to the procedure

After surgery the patients are checked with a smear every three months during the first year then less frequently (Fig 1) Patients are registered in a special filing system which ensures the continous follow up Failure to attend results in a reminder being sent Very few patients are lost to follow up Patients showing persistent cytological abnormalities within one year after the above procedure are treated by cryosurgery The majority of persistent abnormalities are detected at the first smear after biopsy Recurrencies seen

Abnormal Sme r

EXCISIONAL PORTIO BIOPSY
+ENDOCERVICAL CURETTAGE

CIN

2 m ths

Sm

N m l

Ab o l

P l dl
me c t ol

CRYOSURGERY

month

Sm r

N rm l

Abnormal

Co l otl / Biop y

ig 1 Regimen for control and treatment of CIN

after one year receive further curettage and biopsy in order to check the histological diagnosis and to exclude microinvasive or invasive cancer before further treatment is instituted

Cryosurgery is done as an outpatient procedure without analgesia A Spembly PCG 12 N_2O driven cryo unit is used that produce −80 C at the cryodes (*Fig 2*) *The cryodes* are interchangeable a conic tipped cryod is used [illegible] clusively because it fits well into the whole cervix [illegible] firm contact between the tissues and the cryode [illegible] for maximum freezing effect This is facil[illegible] retaining Cusco-speculum in the vagina and two [illegible] forceps holding the cervix at 3 and 9 o clock The [illegible] of the procedure is decided by observing the well [illegible] edge of the frozen tissue on the portio Usually [illegible] application of the cryode will freeze the cervical [illegible] to 10 mm

To begin with we used the single freeze techni[illegible] quently a double freeze technique was used [illegible] reports suggested that better results were achieved [illegible] technique Thus the procedure was repeated [illegible] for 20 min

The procedure has few side effects [illegible] necessitate time off work After four months the [illegible] re enter the follow up system already described with persistent smear abnormalities after cryos[illegible] treated individually taking into account factors [illegible] histological severity progression and the site [illegible] the lesion as well as age and parity and [illegible] gynecological or other complaints Further cryo[illegible] rarely performed most patients receiving cold k[illegible] tion

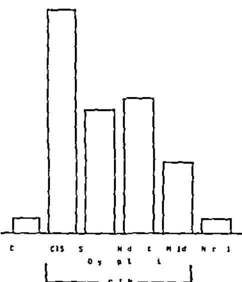
Table I *Results of cryosurgery 93 pat[illegible]*

Diagnosis	Number	Healed	
		Number	Pe[illegible]
Cancer in situ	48	28	[illegible]
Severe dysplasia	30	23	[illegible]
Moderate dysplasia	11	10	[illegible]
Mild dysplasia	4	3	[illegible]
Total	93	64	[illegible]

MATERIAL

Biopsy During the period from May 1st 19[illegible] 1977 198 patients were treated by curettage and [illegible] biopsy Ages range from 17 to 64 the medium [illegible] years Histologically 57 per cent of the [illegible] *classifiable as severe dysplasia or cancer in situ* [illegible]

Fig 2 Instruments used in our regimen Spembly PCG 12D cryo-unit with cryodes Bivalve Cusco self retaining vaginal speculum Hartmann conchotomes diamete 9 and 11 mm Schröder forceps



3 Histological diagnosis 198 patients

5 patients histology were benign and in 5 patients we
d invasive cancer These 10 patients were excluded
ng 188 patients
e time of observation was from 6 to 42 months averag
18 months

Ninety three patients were treated with
surgery These consisted of 62 patients from our own
sy series and in addition 31 patients referred by other
cologists who were treating the patients according to
regimen
istologically 84 per cent had severe dysplasia or cancer
u (Table I)
e time of observation was 7 to 36 months averaging 18
ths

RESULTS

sequent smears were normal in 101 (53 7 per cent)
e 188 patients with CIN (Table II)
ut of the remaining 87 patients showing persistent
logical abnormalities 62 underwent cryosurgery

le II *Results of multiple biopsy 188 patients*

nosis	Number	Healed Number	Healed Per cent
er in situ	76	34	44 7
re dysplasia	42	19	45 [illegible]
erate dysplasia	46	30	65 2
dysplasia	24	18	75 0
l	188	101	53 7

Table III *Results in relation to the site of the lesion in 78 cryosurgically treated patient with CIS and severe dysplasia*

	Ectocervical lesion Number	Ectocervical lesion Per cent	Ecto- and endocervical lesion Number	Ecto- and endocervical lesion Per cent
Healed	45	70	6	43
Non healed	19	30	8	57
Total	64	100	14	100

To these were added the 31 patients referred by other gynecologists Of these 93 patients 64 (69 per cent) had normal smears after one treatment Normal smears were found less often after both biopsy and cryosurgery in the patients with more severe histological lesions (Tables I and II)

The results were considerably better for ectocervical lesions compared to those who also had endocervical changes The difference is statistically significant with $p < 0\ 05$ (Table III)

After cryosurgery the results were better in the younger age groups the patients with normal smears averaging 31 years of age and those showing persistent CIN after cryosurgery averaging 36 5 years

Complications after excisional biopsy and curettage are hemorrhage and infection Two patients had hemorrhages of approximately 300 ml necessitating extra sutures in one tamponade and observation for 24 hours in the other Nine patients had post operative pelvic inflammatory disease (PID) of moderate degree all showing resolution within two weeks on conventional therapy

Complications after cryosurgery are very few no hemorrhage or cervical stenosis have been seen so far One patient was admitted to hospital and was given antibiotics for a severe lower genital tract infection (LGTI) Laparoscopy was performed and PID was excluded Retrospectively the patient had had clinical cervicitis at therapy this should have contra indicated cryosurgery

A side-effect rather than complication is the copious clear discharge which most patients experience after cryotherapy Another side-effect is the short flushing that 60 per cent of the patients experience during the thawing of the frozen tissues It usually involves the upper trunk and extremities in a wave form and there may be a transient headache This may be caused by release of histamin from the

damaged cells Apart from the immediate discomfort above mentioned this has not been associated with any long term problems or other serious side effects

DISCUSSION

In Sweden we have a conservative attitude to the treatment of the uterine cervix The most common *method for treatment of severe dysplasia and car* cinoma *in situ* is a diagnostic and therapeutic coniza tion sometimes as the first measure after an abnor mal cytological smear This method is very effective but can lead to both direct and late complications and necessitates hospitalization

The Swedish nation wide cytological screening pro gramme and the frequent screening of younger women outside the programme has resulted in a sharp increase in the diagnosis of asymptomatic CIN

The peak age incidence for cancer in *situ* and dysplasia (CIN) is between 30 and 40 years (8) and is decreasing (6 7 20) These facts justify our efforts to *find alternative methods of treatment for the young* fertile woman methods combining therapeutic effi ciency and the accurate exclusion of invasivity with few complications and minimal danger to fertility

Our technique using general anaesthesia provides a large and more satisfactory sample of tissue for pathological analysis than when the procedure is done with the patient awake Diagnoses should be ore reliable both for ectocervical as well as for en *cervical changes The risk of missing early invasive* anges is minimized The thorough histological stag ing obtained is of great assistance on the further op- timal treatment of the patients

We get a primary therapeutic effect in half of our patients This corresponds well with other authors (1) and shows how important it is to check the therapeutic effect of biopsies by taking follow up smears before resorting to further treatment We con sider a primary conization based on only one cytological abnormalities an unnecessarily large pro cedure which should be replaced by multiple exci sional biopsies

Our regimen differs from other studies employing cryosurgery (3 21 23 24) The therapeutic effect of alternative treatment of CIN is difficult to assess because biopsy will change the natural course of the disease This means that if biopsy and cryosurgery are performed together it is not possible to measure the therapeutic effect of the two components of treat ment In our series of 188 patients 101 patients had normal cytology after biopsy alone and [illegible] cryotherapy would have been performed in [illegible] cases had the cervix not been reassessed [illegible] biopsies Criticism of the cryosurgical [illegible] severe dysplasia and CIS has occurred largely [illegible] tissue for histological examination is not [illegible] the time of treatment The time interval be[illegible] biopsy and the first post biopsy smear in our [illegible] 2 to 4 months *The total time interval between [illegible]* itial abnormal smear and the first [illegible] cryotherapy is 6 to 8 months Progression to [illegible] cancer in such a short interval is very rare [illegible] theless we do not perform repeated cryotherapy [illegible] persistent cytological abnormalities but prefer [illegible] tion as this provides an accurate histological [illegible] sis For this reason our success rate for cryother[illegible] less than that of other published works [illegible] peating cryotherapy obtain a success rate of [illegible] per cent (4 10 21 23 24) It should be noted these results are often the effects of biopsies [illegible] peated cryosurgery

When comparing our regimen of treatment [illegible] conventional conization we have a lower [illegible] healing (2) This is especially true for older [illegible] and patients with endocervical lesions or a com[illegible] tion of both Conization however is a [illegible] complex procedure involving a stay in ho[illegible] higher rate of complications and the need for [illegible] post operative restrictions on activity Also [illegible] smears are as important after conization as [illegible] *sional biopsy and cryosurgery*

CONCLUSION

By doing multiple extensive biopsies of the [illegible] combined with cervical curettage under [illegible] anaesthesia on an outpatients basis in patients [illegible] cytological CIN we obtain a reliable [illegible] diagnosis as well as a satisfactory therapeutic [illegible] in more than half of the patients

In patients with persistent cytolgical [illegible] CIS after multiple biopsies cryosurgery is [illegible] especially on younger patients with ectocervi[illegible] *sions before resorting* to other methods of [illegible] ment

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The authors wish to thank Ass Professor G [illegible] reading and revising the manuscript

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Acta Obstet Gynecol Scand 59 355–359 1980

IN VITRO INDUCTION OF MURINE SUPPRESSOR T CELLS BY HUMAN CHORIONIC GONADOTROPIN

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Human chorionic gonadotropin (HCG) has ,ously been considered to be immunosuppressive and by prohibiting maternal rejection of the fetal plant to be one of the factors responsible for the suc ful outcome of pregnancy The mechanism by which exerts its pregnancy retaining effect is however as yet own The present study shows that HCG has the ity in mice of inducing lymphocytes which are subse ly competent to depress a polyclonal antibody re e induced by different B cell mitogens It is therefore ted that HCG may exert its feto-protective action by ng suppressor T cells These lymphocytes would thus it the activation of cells which are responsible for lant rejection

nechanism which prevents the fetus a histoin atible graft from being rejected is still an un l problem and although a vast number of ex tions have been proposed none has so far prov onclusive Human chorionic gonadotropin) a glucoprotein produced in large amounts by ophoblastic cells (4) has been shown to sup- mitogen induced proliferation of both T lym tes (1 5 11) and B lymphocytes (2 10 25) these studies it has therefore been suggested ICG is one of the main factors contributing to munosuppression responsible for the survival fetal transplant The mechanism by which exerts its suppressive effect is however still understood

ıa feto protein synthesized in large amounts fetus is another hormone which is suggested sess immunosuppressive properties (24) This ssive effect has been claimed to be due to in n of suppressor T cells (17) This cell type was y described by Gershon and coworkers (9) ggested that certain T cells were involved in pression of a sheep red blood cell specific im esponse To date suppressor cells have been recognized in a variety of systems where they have been shown to impair B lymphocyte responses as in duced by antigens (6) or polyclonal B cell activators (21 22) The immunosuppressive cross reactivity be tween HCG on lymphocytes from other species in cluding mice (2 7 11 14) indicates that animal systems may be used for evaluating the mechanism underlying the suppressive effect of HCG In this paper we de cribe the induction of suppressor T cells in mice by HCG The possible importance of these observations and their clinical implications are con sidered

MATERIAL AND METHODS

Animals Female C3H/Tif mice used at the age of 8–12 weeks were bred and maintained in our animal colony

Cells Spleens were removed aseptically and cell suspensions were prepared by pressing the tissue through a steel mesh in to a balanced salt solution (BSS) After brief sedimentation the non sedimented cells in the supernatant fluid were wash ed with BSS resuspended in culture medium counted and adjusted to appropriate concentrations The viability was determined by trypan blue exclusion

Culture medium Mishell Dutton medium was prepared from components purchased from Flow Laboratories Ir vine Scotland and was supplemented with HEPES buffer All media were supplemented with 5 per cent heat inactiv ated human AB serum

Mitogens Concanavalin A (Con A) was purchased from Pharmacia Fine Chemicals Uppsala Sweden Lipopolysac charide (LPS) from Es herichia Coli 055 B5 was obtained from professor T Holme Dept of Bacteriology Karolin ska Institute Stockholm Sweden Purified protein deriva tive of tuberculin (PPD) was purchased from Statens Se ruminstitut Copenhagen Denmark

Assay of antibody synthesis Antibody production was determined using a modification (21 22) of the original mouse plaque assay system (13) Cells were harvested with a plasti spatula after 2–3 days of culture washed twice in BSS and resuspended in 1 ml of BSS 0 5 ml of 0 5 per cent agar (Difco Laboratories Detroit Michigan USA) in BSS

Table I *Suppressive effect of HCG activated cells*

Exp No	Substance used for preactivation	Mitogen used for activation	IgM anti NNP PFC/cult	Suppression per cent
1	0	LPS	1 375	0
		PPD	1 005	0
	Con A	LPS	40	97
		PPD	4	99 6
	HCG	LPS	450	66
		PPD	40	97
	HCG (2×10⁶ dead precult cells)	PPD	1 050	−4
2	0	LPS	160	0
	Con A	LPS	4	98
	HCG	LPS	16	90
3	0	LPS	1 400	0
		PPD	1 500	0
	Con A	LPS	25	98
		PPD	55	96
	HCG	LPS	800	43
		PPD	790	47
4	0	PPD	235	0
	Con A	PPD	15	94
	HCG	PPD	145	38

Spleen cells *from femal* C3H/Tif mice were cultivated for 48 hours in the presence of 10 μg Con A/ml or 2 000 IE/ml HCG Thereafter the cells were harvested and 2×10^6 *precultivated* cells were mixed with 8×10^6 syngeneic *fresh spleen cel s* *The* admixture was cultured in the presence of 100 μg LPS/ml or 100 *μg PPD/ml* and assayed on day 3 for the *number of anti NNP* plaque forming cells In experiment 1 freeze killed cells were also included as a control

containing 0 5 per cent DEAE *dextran (Pharmacia* Uppsala Sweden) was added to 3 *ml tubes and kept at* 46 C in a *water bath 0 05* ml of target erythrocytes heavily coupled with *NNP* (*4-hydroxy 3 5* dinitrophenacetyl) diluted 1 8 in BSS 0 2 *ml of the* lymphocyte cell suspension and 0 05 ml of guinea *pig complement diluted 1 4* in BSS were added to each tube The *ingredien s were mixed* and evenly *spread on* 9 cm plastic Petri dishes and incubated for 3 hours a 37 C The plaque forming cells (PFC) were counted using indirect light

Nylon wool column filtration T cell separation was performed using a *modification* of the *method* described by Julius *et al* (12) Briefly spleen cells *were added* directly on nylon wool columns 0 6 gram of the wool (*Leukopak Leukocyte* Filters LP 1 Fenwall Lab Chicago USA) *was loosely packed* into 10 ml *syringes (20) The* cells were eluted with BSS supplemented *with 5 per cent* fetal calf serum

Hormones Purified HCG *preservative free* was generously supplied by Leo AB Hälsingborg *Sweden*

Experimental procedure

Lymphocytes *were cultured* for 48 hours in the presence of 10 μg/ml of Con A *or various* concentrations of HCG The cells were then harvested washed in BSS and added in different ratios to fresh spleen lymphocytes The cell mixture was either left untreated stimulated with LPS (100 μg/ml) or with PPD (100 μg/ml) The number of IgM anti NNP SRBC secreting cells was determined on day two or three The *cultures were kept* on a rocking platform a procedure *shown to increase the* suppressive capacity (9)

Table II *Effect of different HCG* concen[illegible] the induction of suppressor cells*

Substance used for preactivation	Mitogen used for activation	Exp 1 IgM anti NNP PFC cu[illegible]	[illegible]
0	LPS	1 400	
	PPD	1 500	[illegible]
Con A 10 μg/ml	LPS	70	
	PPD	60	[illegible]
12 5 IE HCG	LPS	1 040	
	PPD	1 160	[illegible]
250 IE HCG	LPS	675	
	PPD	800	[illegible]
1000 IE HCG	LPS	N T	
	PPD	N T	[illegible]
2000 IE HCG	LPS	800	
	PPD	790	[illegible]

Spleen cells from female C3H/Tif mice were cult[illegible] in the presence of various concentrations of HCG The[illegible] cel s were harvested and 2×10^6 precultivated cells [illegible] 8×10^6 syngeneic fresh spleen cells This admixture was [illegible] the presence of LPS or PPD in a concentration of 100 μ[illegible] res were harvested on day 3 and tested for the number [illegible] plaque forming cells

N T = Not tested

RESULTS

HCG induced suppressor cells Since we h[illegible] ously shown that 2 000 IE of HCG/ml is [illegible] pressive the ability of the hormone used in [illegible] centration to induce suppressor cells was [illegible] can be seen in Table I preculitvation [illegible] splenocytes with HCG resulted in the form[illegible] cells which were capable of inhibit [illegible] activated with lipopolysaccharide or with [illegible] protein derivative The inhibitory capaci[illegible] from 38 – 97 per cent possibly ref[illegible] logical variability Control cells not [illegible] with Con A or HCG did not normally [illegible] magnitude of the response (data not show[illegible]) cond set of experiments various concentratio[illegible] hormone were tested for the induction of s[illegible] cells As can be seen in Table II a con[illegible] 250 IE/ml was sufficient to induce inhibit[illegible] since lower concentrations of HCG were [illegible] duce inhibition in this test system as [illegible] our previous studies it seems as if this [illegible] assay is more sensitive for the detect on [illegible] sion

Cell requirements for HCG induced suppr[illegible] assess the putative T cell character of the HC[illegible] ed suppressor cells nylon wool colu[illegible] cells which are normally highly enrich[illegible] were tested for their suppressive capaci[illegible] either left untreated or precultivated with C[illegible]

ıle III *Suppressive effect of HCG column purified T cells*

ıtance used preactivation	Mitogen used for preactivation	IgM anti NNP PFC/cult		Suppression (per cent)	
		Spleen cells	T cells	Spleen cells	T cells
1 0	LPS	N T	1 300	N T	0
	PPD	N T	1 350	N T	0
Con A	LPS	N T	15	N T	99
	PPD	N T	30	N T	98
HCG	*LPS*	*N T*	*700*	*N T*	*47*
	PPD	N T	710	N T	48
2 0	LPS	1 200	1 400	0	0
	PPD	1 035	1 100	0	0
Con A	LPS	125	50	90	96
	PPD	250	45	76	96
HCG	LPS	470	750	61	47
	PPD	640	600	39	46

cells or column purif ed T cells from female C3H/Tif mice were cultivated for 48 hours in the p esence of 2 000 IE of HCG/ml eafter the cells were harvested and 2×10^6 precult ated cells w re added to 8×10^6 syng ei fresh spleen cells This adm xture was ated in the presence of LPS or PPD in a concent ation of 100 µg/ml Cultures were harvested on day 3 and tested for the number of anti plaque forming cells

3 for two days As seen in Table III these cells capable of inducing a marked suppression of ogen induced B cell differentiation Cytotoxicity not seem to be involved since cell survival was impaired in cultures containing suppressor cells a not shown) Furthermore the immunosuppres did not depend upon transfer of HCG from the iary culture since freeze killed cells mixed with 3 did not diminish the PFC response of secon cultures (Table I) We also investigated the ef of transfer of various amounts of cells precultiv with HCG and as shown in Table IV a ratio of ast 1 10 between suppressor cells and effector was required to induce suppression of the PFC onse

e IV *Effect of various amounts of HCG ac ed cells for suppression*

ıltıvated cells res (%)	IgM anti NNP PFC/cult addition during precultivation	
	HCG 2 000 IE/ML	0
	225	1 200
	600	900
	1 050	1 400
	1 025	1 800
	1 150	1 150

cells from femal C3H/T f mice were cultivated for 48 hours presence of 2 000 IE of HCG/ml Thereafter the cells were ted and an u amou ts of precult ated cells were added t ne f esh spleen cells to result in a f nal concentration of 10^7 ml The adm ture was cult ated in the presence of 100 µg Cult res were harvested o day and tested for the n mbe of NP plaque form g cells

DISCUSSION

The fetus although antigenically foreign is normally not rejected by its mother Many hypotheses have been proposed to explain this biological and immunological paradox but some of the older ideas such as the uterus being an immunologically privileged site antigenic immaturity of the fetus or an anatomical fe to maternal separation may no longer be valid (for discussion see *16*) To date one of the most attrac tive theories which explain the successful feto-mater nal transplantation is the local production of soluble immunosuppressive factors such as human chorionic gonadotropin (1 5 10 11) human chorionic somatomammotropin (5) and alpha feto-protein (24) Since the amounts of HCG adjacent to the trophoblasts exceed the concentrations needed for suppression of immune responses (4) these results argue in favor of the assumption that this hormone may constitute a pregnancy retaining factor The dif ference in concentrations between retroplacental and peripheral blood would then be of importance in protecting the fetus from rejection leaving the overall maternal immunological resistance unimpaired (8)

It is suggested that the mechanism by which alpha feto-protein exerts its putative immunosuppressive ef fect is by the induction of suppressor T cells (17) An tigen induced suppressor cells a distinct subpopula tion of T cells were described in the beginning of the *1970 s by Gershon and coworkers (9 for review see* 18) who showed that specific immunological unre sponsiveness to sheep red blood cells in mice could be passively transferred with lymphocytes

Mitogen induced suppressor cells on the other hand have been shown to inhibit not only specific T cell dependent immune responses (6) but also a polyclonal response as induced by B cell mitogens such as LPS and PPD (21 22) The results presented in this paper suggest that HCG induced cells may act in a similar fashion to those induced by T cell mitogens (concanavalin A) The effect was not due to cytotoxicity since cell survival was not affected nor was it due to passive transfer of HCG since freeze killed cells were nonsuppressive The cells were found to resemble T cells as shown by their capacity to pass through a nylon wool column This is in agreement with earlier findings showing that a majority of suppressor cells are of T cell origin (18) In this study only female mice were used mainly to imitate a natural biological model and also because human fetal cells have previously been shown to suppress a mitogen induced response of the maternal cells (19)

However the feto maternal relationship may be guaranteed not only by means of soluble factors produced by the mother or fetus but also by a complex mechanism with different factors involved all contributing to the successful outcome of pregnancy In this context it may be appropriate to make a direct comparison between pregnancy and some of the genetic factors known to be related to graft survival in surgically transplanted patients In all species major histocompatibility complex encoded products pre ted on the cell surface are responsible for induc n of the homograft reaction In man these co dominantly expressed antigenic markers are determined by genes within one region on chromosome 6 This part of the genome is composed of different loci where the D locus seems to be the most important one for transplant rejection Recent data indicate that the one year survival of kidney transplants in certain instances may approach 80 per cent when donor and recipient share one D locus and thus are mismatched for only one D allele (23) This may be comparable with the feto-maternal relationship where only half of the genetic material is antigenically foreign to the mother and since the frequency of early spontaneous abortions ranges between 15 – 30 per cent (3 15) the successful outcome of pregnancy in most cases may be due to a single D locus dissimilarity but other immunosuppressive factors may contribute (for discussion see 10) The biological relevance of studies in which it is shown that HCG is immunosuppressive can at this stage not be fully evaluated In this study however we demonstrate that one possible mechanism of HCG induced immunosuppression is the [illegible]eration of suppressor T cells theoretically [illegible] to impair transplantation antigen induced [illegible]cyte activation of maternal cells

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GRANULOSA CELL AND THECA CELL TUMORS

The clinical picture and long term outcome for the Radiumhemmet series

Elisabet Björkholm and Folke Pettersson

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ract Over the period 1923–72 a total of 305 patients granulosa-cell theca-cell tumor and mixed tumor were at Radiumhemmet
e commonest symptom was abnormal uterine bleeding ity three per cent of married women were nulliparous menarche seems to have occurred earlier in this group in the general population
ght of the granulosa-cell tumor group gave birth to 12 ren after treatment for the tumor
neteen women with granulosa-cell tumor and 4 with ma had received radiotherapy earlier in life for benign ns
e risk of endometrial cancer was approximately 10 greater for the women with granulosa or theca-cell than for the general population
o hundred and fifty two patients were given both cal treatment and radiotherapy Fifty three received *surgery (37 granulosa-cell and 16 theca-cell tumors)*
ne of the thecoma patients but 21 per cent of those granulosa-cell tumor died from their disease The r survival for the latter group all stages was 85 per

ulosa and theca-cell tumors together constitute argest group of functioning ovarian neoplasms granulosa-cell tumors occur as mixed neo- ns containing both granulosa and theca cells For the 4-year period 1962–65 the annual inci rate for granulosa and theca-cell tumors in len was 1 70 per 100 000 of the female popula this is the highest figure reported by any West ountry (9) Granulosa-cell tumors and thecomas ituted 8 per cent of all ovarian neoplasms d at Radiumhemmet (15) According to other s between 5 and 10 per cent of all malignant an tumors are of the granulosa-cell type (16) nalignant potential of this tumor has been vari reported Novak gave a figure of 25 per cent So far no unequivocal clinical or histologic in of the long term prognosis for the patient has identified Pure theca-cell tumors — thecomas — are almost invariably benign (16) Both granulosa and theca-cell tumors are often estrogenic and a distinctive clinical history of abnormal uterine bleed ing is usual The simultaneous occurrence of the two types of tumors and adenocarcinoma of the endome trium is frequently reported (7)

As a consequence of the centralized organization of cancer treatment in Sweden a relatively large number of women with granulosa and theca-cell tu mors have been treated at Radiumhemmet Stock holm The purpose of this study was to analyze this material from various clinical aspects and to examine the prognosis for the patient with either of these types of tumors

MATERIAL AND METHODS

Between 1923 and 1972 a total of 263 women with histolog ically verified granulosa or mixed granulosa and theca-cell tumors (referred to below as granulosa-cell tumors) and 42 with pure thecomas were seen at Radiumhemmet They had been referred from various parts of Sweden one half of them from the Stockholm area All the histological speci mens were re-examined at the Department of Tumor Path ology at the time of admission All the available en dometrial specimens were also reviewed in connection with this study A follow up of all the patients was performed in 1977–78 This was greatly facilitated by the system of civil registration and personal identification numbers used in Sweden The population registry furnished data on the pa tients including date and cause of death and the name of the physician signing the death certificate which informa tion enabled the patient s subsequent hospital records and autopsy reports to be traced Information from the popula tion registry and the medical reports was punched on cards for statistical analysis The clinical picture was analyzed for the two tumor groups No histological grouping of the granulosa-cell tumors according to cell pattern was made

Statistical methods The survival rate was analyzed with life tables using a computer program The expected survival of a population with the same age distribution as the granulosa-cell tumor series was calculated from life tables for the Swedish female population

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le III *Radiotherapy given earlier in life to the granulosa-cell tumor and thecoma patients*

	Granulosa-cell tumor patients		Thecoma patients	
	No	Interval between diagnosis and therapy year	No	Interval between diagnosis and therapy year
omen	0		1	14
ist region	3	1 4 4	0	
d and neck	3	10 13 18	0	
.ts etc	4	2 3 10 26	0	
acavitary	3	2 3 3	1	19
ration	6	1 2 4 5 5 24	2	13 26
il	19		4	

rhesus groups in 124 cases 87 per cent of whom e Rh positive The distribution by blood group is n in Table II where a comparison is made with the dish population as a whole (8)

liotherapy prior to diagnosis Nineteen women 1 granulosa-cell tumor and 4 with thecoma had ived radiotherapy for benign lesions earlier in The site and the interval prior to diagnosis are ented in Table III

er malignant diseases All malignant diseases were orded either from the patients hospital records or th certificates In the case of a new malignant ase in a patient once treated at Radiumhemmet institution was notified a few malignant tumors found at autopsy Twenty per cent of the nen had at least one such disease the commonest ig endometrial carcinoma with 33 cases of whom ould be reviewed and were confirmed In 29 of n this tumor occurred simultaneously with the rian tumor (Table IV) Nine women had breast er (7 of the granulosa-cell tumor and 2 of the oma groups) A number of other malignant ases were recorded in the remaining patients All patients but one with endometrial carcinoma had ed the menopause the exception was 47 years old had a thecoma

Endometrial alterations Endometrial biopsy reports from the ovarian operation were available for over one half of the patients with granulosa-cell tumor and for three quarters of the thecoma group glandular cystic hyperplasia occurred in 45 per cent of the former group and 13 per cent of the latter

Clinical stage Surgical reports were available for all but one of the patients The tumor was classified as Stage I (FIGO) in 90 per cent of the granulosa-cell tumor patients and in all the thecoma group The tumors were bilateral in 2 and 5 per cent respectively

Tumor si e Where the size of the tumor had been ex pressed by comparison to fruits nuts eggs and the like it was converted into centimeters in diameter (Table V) While the granulosa-cell tumors varied greatly in size they tended to be larger than the thecomas with 42 per cent at least 11 cm in diameter compared with 12 per cent of the thecomas

Treatment The treatment given to these patients has varied over the years In 53 of the 305 patients surgery was the sole measure (37 with granulosa-cell tumor and 16 with thecoma) in the remainder radiotherapy was also given The operative technique ranged from simple resection of the ovary or unilateral oophorec tomy to radical surgery including omental resection The radiotherapy consisted in intracavitary radium or external irradiation or a combination of these Con

IV *Endometrial carcinoma occurring after or aneously with the ovarian tumor*

	Endometrial carcinoma No	
	Total	Co-existing with the ovarian tumor
losa-cell tumor	21	19
ma	12	10
	33	29

Table V *Granulosa-cell tumors and thecomas distributed by si e expressed as the diameter*

	Percentage of tumors						
Tumor diameter cm	1	2	3	5	8	11	20
Granulosa-cell tumors (257)	5	3	7	15	28	28	14
Thecomas (4?)	7	7	24	24	26	7	5

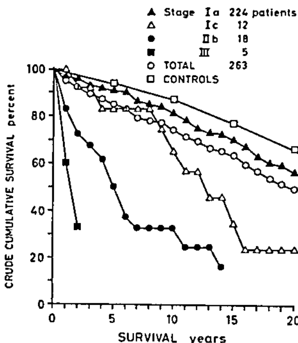


Fig 2 Crude cumulative percentage of survivors for the various clinical stages of granulosa cell tumor compared with the expected survival calculated from life tables for the general Swedish female population

ventional X rays used in the earlier cases were superseded by high voltage techniques

The follow up At the follow up in 1977–78 nearly half of the women were living 60 per cent of them aving a survival time of 15 years or more (range – 47 years) only one woman was lost to the study

In only a few patients was the cause of death veri fied by autopsy the entry in the report being based on the death certificate All deaths from granulosa cell tumor were verified either clinically or histologi cally

Causes of death Twenty-one per cent of the patients with granulosa cell tumor died of the disease and a further 4 per cent had a recurrence these figures serve as an indication of the neoplasm s malignant potential In the granulosa cell tumor group 9 per cent succumbed to other malignant diseases 3 of them to endometrial carcinoma (one of these being diagnosed at the same time as the ovarian tumor) and 5 to breast cancer

In none of the thecoma patients was this tumor the cause of death but 14 per cent died of other malig nant diseases Two deaths were due to endometrial carcinoma (one of them being diagnosed at the same time as the ovarian neoplasm) cancer of the breast colon papilla Vateri and sarcoma of the uterus claimed one patient each The most comm[illegible] of death other than malignant tumor were [illegible] and cardiovascular diseases

Survival The crude cumulative percentage [illegible] vivors for the various clinical stages of the gra[illegible] cell tumor is presented in Fig 2 As a refere[illegible] expected survival curve for a population of [illegible] age structure drawn on the basis of Swed[illegible] life tables is given The outcome was most fav[illegible] for Stage Ia (unilateral tumors) (FIGO) wi[illegible] cent of the patients surviving 5 years and 81 pe[illegible] 10 years The corresponding figures for Sta[illegible] were 50 and 32 per cent The expected figures [illegible] general female population were 94 and 87 pe[illegible] respectively

DISCUSSION

The findings of this study are consistent with the earlier ones as regards age distribution (3 9 [illegible] (12) abnormal uterine bleeding (3 5) age at [illegible] pause (1) and the occurrence of breast can[illegible] There was no evidence of a familial fa[illegible] distribution by blood group did not differ fr[illegible] of the general Swedish population (8)

Most of the patients in this series had reached menarche in the decade 1914–24 To judge fr[illegible] reference figures for the general population [illegible] time (17) the mean age at the menarche for the [illegible] en in our series seems to have occurred [illegible] earlier than the average

Of the premenopausal women with gra[illegible] tumor 16 per cent had a history of secondary [illegible] rhea An annual incidence of 3 3 per cent ha[illegible] reported in a randomly selected Swedish pop[illegible] in the age range 18–45 (14)

The number of nulliparous married wom[illegible] granulosa cell tumor was three times great[illegible] reported by Kolstad & Beecham (1975) [illegible] mean for Norwegian married women (9) The [illegible] tionship between hormone secreting tumors [illegible] ovary and sterility is difficult to qua[illegible] great majority of women with such tumors [illegible] child bearing age It should be noted how[illegible] child bearing may be possible after treatm[illegible] granulosa and theca-cell tumors and the [illegible] may sometimes be cured

In view of the evident connection be[illegible] dometrial cancer and granulosa or theca-[illegible] endometrial biopsy specimens would [illegible] contain information on precancerous chang[illegible]

lometrium Glandular cystic hyperplasia of the en
metrium was common among the patients in the
nulosa cell tumor group but much less so in the
coma group probably because its potential
elopment is masked by the presence of en
metrial carcinoma in many of these patients From
age adjusted expected incidence rates (Swedish
ncer Registry 1965) it would seem that the patient
h a granulosa or a theca-cell tumor runs a ten fold
ater risk of developing endometrial carcinoma
) It is often argued that because of the difficulty
reaching a correct diagnosis in a patient with
ong hormone stimulation of the endometrium
ny of the diagnoses of endometrial carcinoma in
tients with granulosa or theca-cell tumors may be
orrect All but 3 of the observed 33 cases in the
sent series were reviewed and confirmed 5 women
d from the disease Carcinomatous changes in
ier types of cancer are probably due to years of ex
sure to irritants or to substances inducing hyper
sia In the case of endometrial cancer estrogen is
nost certainly involved For a reliable evaluation of
s causal relationship the types and amounts of
rogen produced by the tumor must be known

It is recognized that granulosa cell tumors can be
luced in mice by irradiation (6) There are specific
orts of women who had received radiotherapy
ntually developing granulosa or theca-cell tumors
,10) As many as 7 per cent of the present series of
nulosa-cell tumor patients had at some time
dergone radiotherapy In one half of these (gyne
ogical complaints) the radiotherapy may have been
en for symptoms evoked by the yet undetected tu
r

The survival rate for the granulosa-cell tumor pa
its was slightly worse than that for the general
pulation The stage of the tumor has proved to be
important prognostic factor

The fact that 21 per cent of the women with granu
a-cell tumor died from the disease is clear evidence
its malignant nature

Though a few malignant thecomas have been re
ted their existence is widely doubted (16) None
he theca-cell tumors in this series proved to be ma
nant

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the King Gustaf Vth Jubilee Fund
Ve thank Dr Claes Silfverswärd for reviewing the en
netrial biopsy specimens

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SHORT COMMUNICATION

RELIEF OF MENSTRUAL DISCOMFORT AND DYSMENORRHEA AND SIMULTANEOUS SUPPRESSION OF UTERINE ACTIVITY BY ISOXEPAC

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steroidal anti inflammatory agents used for the tment of dysmenorrhea have already been the ect of a special meeting (1) confirming their im ance in modern science (3) Although it has not i possible to differentiate between the analgesic specific effects of these agents on muscle iophysiology it is nevertheless clear that such pounds decrease both pre menstrually elevated taglandins and high uterine activity (4) Isoxepac -dihydroxy 11-oxodibenz (b e) oxepin 2 acetic is a new non steroidal anti inflammatory agent a marked difference between the dose which vs anti inflammatory properties and that which es gastrointestinal irritation (2) Isoxepac might be suitable for the treatment of menstrual omfort as well as primary dysmenorrhea

single blind study was conducted on the first day ienstrual bleeding to determine the effect of isox on menstrual discomfort in ten normal gravid volunteers (age 22 ± 1 years mean ±SE) on dysmenorrheic pain in eight patients (30 ± 3 s para 0 5 ± 0 3) The patients were not taking contraceptives and no organic cause of the ienorrhea was found In order to exclude pa s with abnormal basic endocrinology plasma esterone and estradiol 17β were analyzed by RIA cycle day 1 Intra uterine pressure (IUP) was rded for 210 min to study the effect of a pro- andin synthetase inhibitor isoxepac on uterine tion in normal and dysmenorrheic patients r a 30 min adjustment period the placebo effect recorded for 1 hour and the isoxepac effect for 2 s Isoxepac was used as a single oral dose of 200 (7 cases) or 600 mg (11 cases) No side-effects observed Significant relief of pain occurred isoxepac administration p < 0 001 (Table I) lower dose of 200 mg was as effective as the 600 lose Ninety minutes after the administration of pac only one case under psychiatric therapy was still having moderate pain Pains if they returned recurred on the average 6 hours after a single dose of isoxepac

Analyses of intrauterine pressure during placebo and isoxepac treatment showed the same basic trend as that observed when other prostaglandin synthetase inhibitors were used (4)

One normal woman with a high active pressure (amplitude) but with a low frequency of cycles and with a low resting pressure (tone) experienced only menstrual discomfort Fig 1 After a single dose of 600 mg isoxepac active pressure decreased and the menstrual discomfort disappeared 30 min after its administration The high active uterine pressure did not cause dysmenorrhea because the low resting pressure and low freuquency of cycles guaranteed normal uterine blood flow (1 4)

One normal woman had abnormally high plasma progesterone (5 5 ng/ml) and estradiol 17β (0 13 ng/ml) levels on the first day of bleeding Uterine ac tivity was negligible (Fig 2) as compared with the average IUP found Table II This case was therefore not considered in later statistics As shown in Fig 3 in a dysmenorrheic woman isoxepac reduced all pa rameters of IUP active pressure (AP) frequency of cycles (F) and resting pressure (RP) Average changes in IUP followed a similar course in normal and dys menorrheic women Table II

The reduction of IUP by isoxepac was also statistically significant ($p < 0.05$) in normal women when every patient was considered as her own con trol

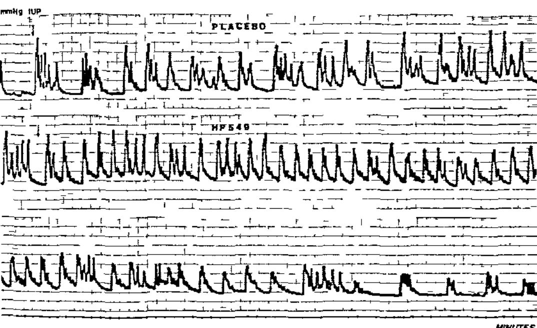
Isoxepac a new non steroidal anti inflammatory agent relieves menstrual discomfort dysmenorrheic pain and reduces uterine activity during the menstrual period It can be considered as a new alternative when the problems of menstrual discomfort and dysmenor rhea a major social problem must be faced by gynecologists

mmHg IUP
200
100
0
PLACEBO
200
100
0
HP549
200
100
0

Fig 1 Note the high active pressure (amplitude) but low frequency of pressure cycles and low resting pressure (tone) This normal woman experienced only menstrual discomfort relieved by isoxepac (HP 549) [illegible] scale minutes

mmHg IUP
200
100
0
PLACEBO
200
100
0
HP549
200
100
0
MINUTES

Fig 2 The very low uterine activity in this normal patient was found to be coincident with high plasma progesterone (5 5 ng/ml) and estradiol 17β (0 13 [illegible]) [illegible] of bleeding



3 Isoxepac (HP 549) 600 mg oral reduced all parame of intra uterine pressure in this dysmenorrheic woman relieved her pain

le I *Relief of menstrual discomfort or pain by isoxepac*

	Before treatment	Placebo treatment	Isoxepac 1st hour	Treatment 2nd hour
rols (10)	2 0±0 7	1 9±0 7	1 5± 07	1 1± 03
nenorrheic (8)	3 4± 15	3 3± 12	2 8± 12	1 7± 11

0 001 Mean±S E (n) Score 1 = no pain 2 = discomfort 3 = moderate 4 = severe 5 = very severe pain

le II *Intra uterine pressure in normal and dysmenorrheic women during isoxepac treatment*

	Resting pressure mmHg	Active pressure mmHg	Frequency of pressure cycles in 30 min
nal (9)			
acebo	23±3	63±12	28±6
oxepac 2nd hour	17±2	51±7	20±4
nenorrhea (8)			
acebo	30±3	59±6	14±1
oxepac 2nd hour	21±5	44±4	10±1

0 05 Mean±SE (n)

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CASE REPORT

PERINATAL ASPHYXIA IN SPITE OF A NORMAL CARDIOTOCOGRAM AND A NORMAL ACID BASE STATE AT THE TIME OF DELIVERY

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tract The labor preceding delivery of a depressed nate with normal acid base status is described Car ocographic (CTG) monitoring was used during the 5 5 rs of active labor Continuous tissue pH determination performed during the last 100 minutes of labor Al igh the CTG pattern was normal all the time tissue pH ined to 7 0? one hour before delivery but reached nor values thereafter The depression of the neonate could be explained by the episode of acidosis one hour before ery

iough most cases of asphyxia can be detected by liotocography some newborns may be delivered i asphyxia and a low umbilical artery pH in spite cardiotocogram which has appeared normal dur labor (4)

urthermore although the fetal pH at delivery cor es very well to the Apgar score (3) a normal acid state in the blood of the umbilical vessels can be id in depressed neonates (1) The depression may caused by drugs infections airway obstruction enital anomalies precipitous delivery prematu and also by a previous episode of asphyxia very of acid base state but not of the responsive of the central nervous system)

ie following case illustrates that the last cause tioned by James *et al* for a lack of agreement een the Apgar score and the acid base state of the born is not only theoretical The case also il ates that the cardiotocographic pattern can be nal in spite of a decreasing tissue pH

CASE REPORT

year-old para 2 with a pregnancy which was normal the 36th week of gestation was admitted to our depart because of decreasing HPL (human placental lac) values but normal estriol values As the HPL values remained low labor was induced by artificial rupture of membranes (ARM) Two hours later the contractions were stimulated by oxytocin (4 to 12 mU/min during the first stage of labor and 16 to 20 mU/min during the second stage of labor total amount of oxytocin 5 Units) At the same time cardiotocography was initiated using an internal spiral ECG electrode and external registration of the contractions Five hours after ARM epidural analgesia was started using an epidural catheter because of painful contractions No analgesics or other drugs than oxytocin were used An hour later (6 hours after ARM) the cervix was dilated 5 cm and a pH electrode was applied together with an intrauterine cath eter (2) The course of the rest of labor was uneventful the second stage only lasting 10 minutes The total duration of labor (from ARM) was 7 5 hours

The CTG was normal before induction of labor during the beginning of induction and throughout the first stage of labor Figs 1 – 3 show a normal CTG with isolated ac celerations simultaneous with the contractions a normal base line and variability and very few early decelerations especially during the last 30 minutes of the first stage Dur ing the second stage which lasted only 10 minutes the baseline declined from 140 to 120 beats per minute and the early decelerations became more pronounced but the fetal heart rate reached the baseline level again immediately after the contractions

The tissue pH was registered for the first time 100 minutes prior to delivery (Fig 1) Fig 1 shows the decrease of pH from 7 22 to 7 02 during the first 30 minutes of pH monitor ing As this decline was thought to be a false low pH reading (CTG normal) and as a low tissue pH in itself at this stage of the investigation is not an indication for obstetrical in tervention there was no interference During the next hour (Figs 1 and 2) the pH increased reaching a maximum level of 7 28 (Fig 2) During the second stage (Fig 3) the pH decreased from 7 28 to 7 21 the last value corresponding very well to the umbilical artery pH of 7 24 (umbilical vein pH 7 31) The other acid base values and the oxygenation of the umbilical artery were also normal (base excess – 5 0 mmol/l pCO_2 56 mm Hg standard bicarbonate 17 8 mmol/l pO_2 9 mm Hg oxygen saturation 16 per cent) when measured on autoanalyzers (ABL 2 and OSM 2 both Radiometer Copenhagen)

A cyanotic hypotonic infant was delivered Apgar scores were 2 8 and 10 respectively one three and five minutes

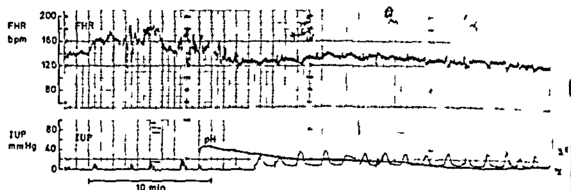


Fig 1 Cardiotocogram (CTG) including tissue pH values 75 – 115 minutes before delivery The CTG showed a normal baseline level and variability and a few early decelerations (maximum 15 beats per minute) The acceleration before tissue pH registration is caused by the [illegible] the pH electrode The pH was 7.23 at the time of [illegible] tion 25 minutes later the pH had decreased to 7.[illegible] end of the period the pH was 7 05

after delivery Birthweight 2 900 g length 51 cm The infant was admitted to the intensive neonatal department because of respiratory distress and perinatal asphyxia Oxygen and CPAP (Continuous Positive Airway Pressure) treatment was necessary until the infant was three days old On the seventh day the child was discharged with a normal neurological status No infections anomalies or other explanations for the perinatal depression were found

DISCUSSION

The case illustrates that intrauterine acidosis can develop without the CTG being abnormal The very of a depressed but otherwise healthy infant with a normal acid base state could not be explained by drug administration during labor The episode of acidosis one hour before delivery could [illegible] plain the neonatal depression as it has [illegible] reported that the central nervous system [illegible] depressed for a certain period after normal[illegible] the acid base equilibrium (1)

If more cases similar to the one registered in the future this would be strong [illegible] of the need for tissue pH monitoring in all [illegible] monitored with cardiotocography as ca[illegible] phy cannot always reveal asphyxiation of [illegible] This however requires a better pH mea[illegible] tem in particular one which does not give [illegible] pH values because the risk of such false [illegible] values makes it impossible to intervene when pH reading is the only sign of fetal distress

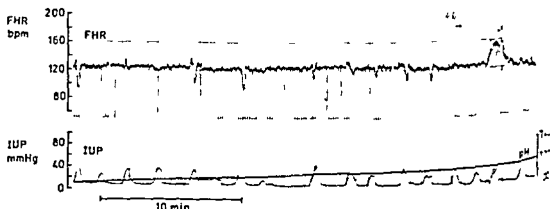
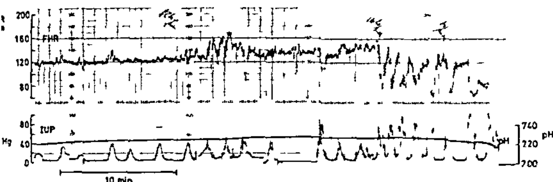


Fig 2 Cardiotocogram (CTG) including tissue pH values 40 – 75 minutes before delivery The CTG showed a normal baseline and variability and a few early decelerations (maximum 25 beats per minute) The acceleration was [illegible] a vaginal examination The tissue pH increased [illegible] 7.20



3 Cardiotocogram (CTG) including tissue pH values 40 minutes before delivery (the last 10 minutes represent second stage) First stage normal baseline level and ability and a few early decelerations (maximum 50 beats minute) *Second stage the baseline decreased from 140* to 120 beats per minute normal variability and early decelerations (maximum 60 beats per minute) The tissue pH reached a maximum of 7 28 at the beginning of the se cond stage thereafter decreasing to 7.22 during the rest of *the second stage The umbilical artery pH was 7 24*

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CASE REPORT

GAUCHER S DISEASE IN PREGNANCY ASSOCIATED WITH INTRA UTERINE GROWTH RETARDATION

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cher s disease associated with pregnancy is rare 33 cases have been reported (3)

ie disease was originally described by Gaucher in and he thought it was caused by a primary n epithelioma It is now known that the disease inborn error of intra-cellular metabolism char rised by abnormal storage of cerebrosides in the ulo-endothelial cells (1)

riginally it was believed that therapeutic abortion indicated when pregnancy was superimposed on cher s disease This has since been refuted use no significant increase in the number of orrhagic complications of pregnancy labor or puerperium have been found

e present a patient first diagnosed as having cher s disease in pregnancy because she develop- hemorrhagic complications and a progressive ease in the growth rate of the fetus Spontaneous rovement in the platelet count which occurred 33 to 38 weeks coincided with improved foetal vth

possible association between Gaucher s disease its haemorrhagic complications and intra ine growth retardation is therefore suggested

CASE REPORT

patient aged 30 years was of Jewish South African n and was 22 weeks pregnant in her first pregnancy n she was admitted with vaginal bleeding She gave a ry of recent onset of rectal bleeding and bleeding from gums

n examination her wieght was 69 8 kg she was not jaun d there was a conjunctival haemorrhage of the right eye peri-orbital bruising as well as marked bruising of the knee The uterus was the correct size for dates and the n was easily palpable

e haemoglobin was 11 8 g/dl white cell count 8 4 x l, platelets 100 x 10^9/l The clotting factors and blood were normal

Her father was known to have an aplastic anaemia of one year s duration and her sister had been diagnosed as having Gaucher s disease

A bone marrow biopsy was performed which showed typical Gaucher cells

The vaginal bleeding stopped no further bruising occurred and she was therefore discharged her platelet count being 125 x 10^9/l

The was readmitted when 29 weeks pregnant with further bruising the platelet count being 95 x 10^9/l Her weight was 69 5 kg and clinically the uterus was small for dates

Her weight continued to fall and at 33 weeks she reached her lowest weight of 68 2 kg Her platelet count also fell progressively to 70 x 10^9/l

From 33 to 38 weeks she gained weight slightly her weight reaching 70 8 kg Over the same period her platelet count improved spontaneously rising to 130 x 10^9/l Serial ultrasound biparietal diameter measurements showed an improved growth rate from 33 to 38 weeks

At 38 weeks a lower segment Caesarean section was performed A live healthy male infant weighing 2 01 kg was delivered The placenta weighed 440 g and blood loss at Caesarean section was 700 ml The post-operative course was uncomplicated She was discharged on the 12th post operative day her platelet count being 175 x 10^9/l She weighed 64 2 kg which had been her non pregnant weight The baby developed no neonatal complications

COMMENT

Previous authors (1 3) have concluded that in cases of Gaucher s disease in pregnancy if close hematological investigation is undertaken a normal antenatal course can be expected with a good fetal outcome

Our patient is extremely interesting in that she presented during pregnancy for the first time with hemorrhagic complications and indeed this led to the diagnosis of Gaucher s disease first being made In addition the growth rate of the fetus decreased markedly from 28 to 33 weeks which coincided with a progressive fall in platelet levels Improvement in the fetal growth rate also coincided with a spontaneous

increase in the platelet count from 33 to 38 weeks It is also of interest that her total weight gain in pregnancy was only 6 2 kg

ACKNOWLEDGEMENTS

We wish to thank Mr P Chalk for allowing us to present this case and Miss L Epsztejn for her assistance in preparing this paper

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CASE REPORT

A MINOR COMPLICATION OF CRYOSURGERY — OCCLUSION OF THE CERVICAL CANAL

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tract In a series of 145 patients who underwent surgery of the cervix uteri six cases (4 per cent) were ıd with occlusion of the cervical canal The patients plained of constant pains resembling labor Inspection ıe cervix uteri showed necrosis covering the orificium mum uteri On removal of the necrotic area there was a ıarge of watery fluid The patients were then free of

ıng the last decade cryosurgery has been increas- y used in the treatment of benign and premalig t conditions of the vulva vagina and cervix uteri treatment usually involves no discomfort for the ent is quick easy and painless and may there be performed on an outpatient basis

s cryosurgery gives satisfactory results and suffers a few complications its application will probably ome even more widespread

t what follows we will describe one of the minor plications which we have called the plug syn ne and which has been described in the literature once before This syndrome has occured in 4 per of our 145 patients

MATERIAL AND METHODS

material consists of 145 patients who underwent cryo- ry of the cervix uteri for slight to moderate dysplasia of these patients (4 per cent) developed symptoms cor onding to the plug syndrome

the time of treatment none of the patients suffered any gynecological complaints and menstruation was lar in all There were no signs of salpingitis vaginitis or r infections Cryosurgery was performed at an arbitrary t in the patient s menstrual cycle but the treatment was poned if there was a possibility of pregnancy

e cryosurgery was done with a cryopistol (Spembley 1°R) powered with nitrous oxide (N_2O) The patients randomized to either one or two sessions of cryosur of one to three minutes per session and the aim was to ve a frozen zone which extended at least three meters beyond pathological areas When the cryo- surgery was performed in two sessions there was a thawing period of four minutes between sessions

After completion of the cryosurgery the ice ball on the cervix thawed in the course of five to fifteen minutes At that stage the macroscopic appearance of the portio was unchanged from its appearance before treatment During the first twenty four hours after cryosurgery patients experienced a profuse watery discharge which continued for two to six weeks After one to three days there was necrosis of the superficial part of the portio that had undergone cryosurgery The necrotic tissue sloughed spontaneously after one to two weeks The portio healed completely during the next few weeks

CASE REPORTS

Case 1 A 30-year-old woman with moderate dysplasia Cryosurgery was performed in two sessions of 85 seconds interrupted by a period of spontaneous thawing lasting four minutes

The patient presented on the third day after treatment complaining of powerful pains resembling labor There had been no vaginal bleeding but as expected there was a profuse watery discharge

Inspection of the cervix showed a large area of necrosis covering the entire central part of the portio including the ostium Vaginal exploration showed normal condition in the pelvis The necrotic tissue was removed without difficulty revealing the ostium There was an immediate escape of watery fluid mixed with a small amount of dark blood The pains disappeared following removal of the necrosis and the patient remained pain free

Menstruation like bleeding occurred for a few days corresponding to the expected time of menstruation The patient subsequently experienced a watery discharge for three weeks

Case 2 A 23 year-old woman with mild dysplasia Cryosurgery was performed in one session lasting 1.0 seconds

The patient presented on the third day after treatment complaining of pains resembling labor There had been no vaginal bleeding but there was the usual watery discharge

Inspection of the collum showed a large area of necrosis covering the ostium Vaginal exploration showed normal conditions in the pelvis The necrotic tissue was removed easily and a small amount of watery fluid escaped The pains then disappeared

There was a normal menstrual period at the expected time three weeks after treatment A watery discharge continued for three weeks

Case 3 A 35 year old woman with *mild dysplasia* Cryosurgery was performed in two periods of 120 seconds each separated by a period of spontaneous thawing lasting four minutes

The patient presented on the fourth day after treatment with complains of indisposition abdominal pain and malodorous discharge

Inspection of the collum showed a large area of necrosis covering the ostium Vaginal exploration showed normal conditions in the pelvis The pain disappeared on removal of the necrotic tissue After vaginal douching with a solution of chloramine for a few days the offensive odour disappeared

There was a normal menstrual period at the expected time ten days after treatment The watery discharge *persisted* for five weeks

Case 4 A 23 year-old woman with mild dysplasia *Cryosurgery* was performed in one session lasting 130 seconds

The patient presented on the sixth day after treatment complaining of pains resembling labor which had *developed* immediately after cryosurgery There had been *no* vaginal bleeding but there was a profuse watery discharge

Inspection of the cervix showed a large area of necrosis Vaginal exploration showed normal conditions in the pelvis The pains disappeared on removal of the necrotic tissue

There was a *normal menstrual* period at the expected time 15 days after *cryosurgery The watery discharge* continued for three weeks

Case 5 A 55 year-old woman with mild dysplasia three *years after the menopause* Cryosurgery was performed in one session of 90 seconds

The patient did *not present herself* in the department again until the agreed time of clinical follow up which was eight weeks after treatment Here she stated that she *had* been troubled by severe pains resembling labor during the *first* two weeks after treatment The pains disappeared *spontaneously There* had been no periods of bleeding or fever At the follow up examination the patient was symptomfree and the physical examination showed normal conditions *The watery* discharge lasted for two weeks

Case 6 A 34 year-old woman with mild dysplasia *Cryosurgery* was performed for a period of 105 seconds

The *day after* treatment the patient was admitted to hospital with the diagnosis acute *abdomen with pronounced* abdominal pain no vaginal bleeding *but watery* discharge Her general condition was unaffected *and her* temperature was normal Inspection of the cervix showed *an approximately one centimeter thick* translucent necrotic *area covering the ostium* Vaginal exploration *showed that* the uterus was normal in size mobile and moderately tender There were no mass or tenderness at the sides On *admission* the patient was put on antibiotic treatment for *suspected commencing* inflammatory adnexal disease

The *gynecological examination* on the eighth day showed that the necrotic area had slought and that *the portio was* healing with a well-defined ostium There were now *no further* complaints about pain

At no time during hospitalization was there any sign of inflammation the temperature was normal and other organ functions *were found to be* normal There was a [illegible] menstrual period at the expected time [illegible] treatment The watery discharge lasted for [illegible]

DISCUSSION

All six patients experienced pains [illegible] one to three days after the cryosurgery The [illegible] condition of the patients remained unaffected [illegible] *their temperature* was normal There was a [illegible] discharge as in the case of other pa[illegible] cryosurgery In four patients a slight [illegible] cient to remove the necrotic area from [illegible] one piece Immediately after its removal [illegible] watery discharge from the uterus and pa[illegible] mediately In patients Nos 5 and 6 [illegible] sloughed spontaneously after which [illegible] *peared In* patient *No* 5 no occlusion of the [illegible] was observed but the case has nevertheless bee[illegible] cluded on account of the typical symptoms

In these patients the characteristic fea[illegible] pain which developed when the ostium bec[illegible] cluded As soon as a passage was established [illegible] the cervical canal by removal or slough[illegible] necrotic plug the pain *disappeared* [illegible] There can hardly be any doubt that the [illegible] described which we have called the [illegible] drome is due to acute hematometra The condition develops because the necros[illegible] ed by cryosurgery can obstruct the cervical ca[illegible] complication is not serious as the pa[illegible] in the course of one to two weeks w[illegible]

Galt (3) in 1975 described a single case [illegible] hematometra following cryosurgery Th[illegible] presented the day after treatment com[illegible] severe abdominal pains A probe was p[illegible] cervical canal and about 15 ml hemorrha[illegible] escaped after which the patient was [illegible] This is the only case mentioned in the [illegible]

Creasman *et al* (1) have reported [illegible] fection following cryosurgery in a series [illegible] tients Two of these patients presented [illegible] of the first week after treatment compl[illegible] abdominal pains The patients were afe[illegible] cological examination showed tenderness [illegible] adnexa for which the patients received [illegible] treatment The appearance of the cervix [illegible] described The course was *otherwise* [illegible] plications These two cases could be exam[illegible] plug syndrome

is conceivable that the development of the g syndrome might depend on the stage of the strual cycle when the cryosurgery was performed rth (2) finds it important to perform cryosurgery ig the proliferative phase of the cycle in order to d hematometra There were no complications in eries of 59 patients

carrying out cryosurgery we have not taken the of the menstrual cycle into account In the six ents with plug syndrome the relationship be n time of cryosurgery and the menstrual cycle as follows one patient had had her menopause years previously one patient had just ceased truating when the cryosurgery was performed underwent cryosurgery around the time of ation (two preovulation date one postovulation one underwent premenstrual cryosurgery As other 139 patients in our series also underwent urgery at a random time in the cycle it may be ned that this took place during the postovulatory e in about half of the patients without giving rise y problems We feel justified in concluding that evelopment of the plug syndrome is indepen of the time at which cryosurgery takes place in trual cycle

Even though it does not represent a serious com plication since the patients will recover spontaneous ly during the course of one to two weeks we have nevertheless considered it important to draw atten tion to the syndrome as these patients can very easily be helped to avoid pain unnecessary treatment with antibiotics and in some cases unnecessary hospitali zation

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CASE REPORT

TORSION OF THE INTERNAL FEMALE GENITAL APPARATUS

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tract A case of a huge right sided ovarian cyst ciated with torsion of the whole internal female genital aratus around the uterine collum herniation of the sverse colon into the thoracic cavity and mechanical ruction of the ileum is described The symptomatology iogenesis and treatment of the condition is discussed

sion of pediculated ovarian cysts fallopian tubes mal ovaries adnexa and sactosalpinges are well ribed disorders (1 2 4 5) Pulmonary complica is of large ovarian cysts have also been reported in literature (3) However common textbooks do describe torsion of the whole internal female ital apparatus as a complication of ovarian cysts and no specific information is available on this dition Further herniation of the colon through rgagni s foramen has not previously been describ- is a complication

We therefore consider it worth while presenting the following case of torsion of the uterus fallopian tubes and both ovaries around the uterine collum complicated by diaphragmatic herniation of the transverse colon through Morgagni s foramen

CASE REPORT

The patient was a 77 year old female admitted because of intermittent abdominal colic localized to both hypochondric regions Apart from operation for a femoral hernia at the age of 56 years she had previously been in good health

During the past two years she had noticed a gradual swelling of the abdomen and in the last 5 months before admission she had had intermittent colic in both flanks and episodes of constipation An intravenous pyelogram performed 4 months before admission was normal

Because of increasing colic she was admitted as an emergency





1 Chest radiographs in the postero-anterior (a) and lateral (b) projections demonstrating herniation of the transverse on into the right hemithorax



Fig 2 Section of colon radiograph demonstrating a hernial ring at the site of Morgagni s foramen

Inspection and palpation of the abdomen revealed a fluctuating mass extending from the symphysis pubis to the xiphoid The patient had slight orthopnoea but was in good general condition Pelvic examination revealed a medium sized rectocele and a small atrophic uterine portio The uterus could not be separated from the abdominal mass on bimanual palpation The preoperative work [illegible] an electrocardiogram which was normal [illegible] radiological examination of the colon [illegible] The chest X ray showed a large part of th[illegible] located above the diaphragm in the right [illegible] 1a and 1b) The colon radiogram sh[illegible] on and a hernial ring on the transverse co[illegible] localized to Morgagni s foramen in the [illegible]

The patient developed increasing symptoms [illegible] obstruction with nausea and vomiting [illegible] celiotomy

At operation a huge cyanotic right sided [illegible] cupying most of the abdominal cavity was [illegible] was emptied of 10 liters of brownish fluid [illegible] that the huge right sided ovarian cyst as well as [illegible] and the left adnex had been torqued [illegible] lower portion of a long atrophic collum [illegible] hemorrhagic infarction of the whole internal [illegible] apparatus A well-defined line of dema[illegible] vital and necrotic tissue on the uter[illegible] The [illegible] uterine and cardinal ligaments were atrophic [illegible] dominal hysterectomy with bilateral salp[illegible] tomy was performed The specimen is shown in Fig 3

The transverse colon was easily pulled back [illegible] domen along with the hernial sack [illegible] after which a 5 x 3 cm large defect in the diaphragm [illegible] site of Morgagni s foramen was closed (Fig 4) A [illegible] portion of the ileum a conglomera[illegible] of [illegible] separated dilated from collapsed ileum The [illegible] divided upon which the intestinal [illegible]

Microscopy of the removed genital apparatus [illegible] hemorrhagic necrosis of a multilocular right [illegible] cyst the uterus and proximal collum the [illegible] and the left ovary The amount of necros[illegible] ment of the presence of malignancy

The postoperative course was uneventful [illegible] wound infection



Fig 3 Specimen removed at abdominal hysterectomy with bilateral salpingo-oophorectomy Note the large right sided ovarian cyst (emptied) the necrosis of the whole internal genital apparatus and the line demarcating vital from necrotic tissue in the uterine collum

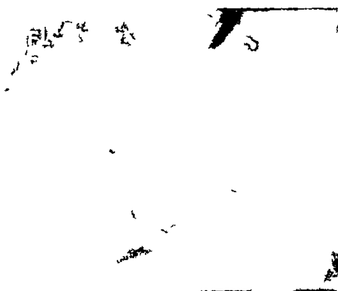


Fig 4 Peroperative picture demonstrating the hernial ring of the enlarged Morgagni s foramen L Liver FL Falciform ligament of the liver P Pericardium seen from the abdomen through Morgagni s foramen

DISCUSSION

sion of the internal female genital apparatus is an em ly rare condition The symptomathology of syndrome can probably not be distinguished from of simple torsion of a pediculated ovarian cyst the present case the size of the cyst had led to placement of the transverse colon into the thoracic ity through Morgagni s foram n However the ient s main symptoms were caused by the hanical obstruction of the ileum due to the adhe

We ascribe the pathogenesis of the condition to be rimary torsion of the large right sided ovarian

The momentum of this torsion on the uterine col along with the weak sacro-uterine and cardinal ments responsible for the fixation of the collum of uterus had eventually led to torsion of the whole ital apparatus

Treatment of the condition is total or subtotal terectomy with bilateral salpingo-oophorectomy oon as the diagnosis has been established since orrhagic necrosis of the genital apparatus with sequent risk of infection may rapidly prove fatal

ACKNOWLEDGEMENT

We thank Kirsten Folke M D Head of the Department of Radiology for kind permission to use the radiographs

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PREMATURE RUPTURE OF THE MEMBRANES

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ract The etiology of premature rupture of the memb- (PROM) has been investigated in 30 consecutive cases 0 matched controls The significance of several possib- tors predisposing to this condition is discussed and the tric and pediatric outcome reviewed S gnificantly inc d frequencies of previous genital operations cervical tions and lacerations were found in the PROM group also contained significantly more heavy smokers The on between the length of the PROM delivery time in and the risks of prematurity and infection are discus 'atients delivered > 24 hours after PROM had signifi more puerperal infections than those with a latent pe f < 24 hours Maternal fever was found to be an un le prognostic indicator The incidence of puerperal in amounted to 27 per cent in the PROM group A 12 nt incidence of proven neonatal septicaemia contribu a high perinatal mortality rate (17 6 per cent)

previous studies have attempted to elucidate athogenesis of premature rupture of the mem s (PROM) but so far no sole causative factor een found Among the explanations suggested echanical factors including poor support such it traumatic cervical incompetence combined increased intra uterine pressure Primary or larily acquired defects of the fetal membranes lso been assumed to be causes of PROM

purpose of the present study was to reveal estic factors with a possible causative relation PROM Since infection following PROM is a nt threat to mother and child the project also d an investigation of the microbiological flora genital tract in these patients with the underly umption that a PROM related infection is not nly a complication but might possibly be of ical significance The hypothesis that as a con e of infection the membranes may become and subject to premature rupture has earlier uggested by Knox & Hoerner (17) and bke (5)

PROM is defined as spontaneous rupture of the amniochorionic membrane prior to the onset of uterine contractions In this paper we report on the clinical findings the microbiological results are published elsewhere (12)

MATERIAL AND METHODS

Patients

Mothers All patients with PROM before the 36th week of gestation 30 in all admitted to the Department of Obstetrics and Gynecology during the period July 1976 to October 1977 have been included in the study Every patient was matched with a control as regards age parity duration of pregnancy and socioeconomic status (all middl class)

The age distribution of the patients is shown in Fig 1 PROM was diagnosed by means of vaginal examination which was sometimes confirmed by cytological examination for fetal cells using the Nile blue sulphate staining procedure described by Kittrich (16) Antenatal birth weight was es-

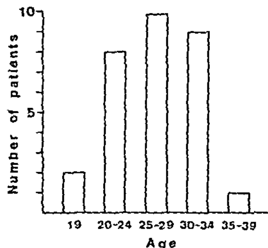


Fig 1 Age distribution of patients

Table I *Previous genital operations*

	PROM	Controls
Exaeresis after spontaneous abortion	4	6
Legal abortion suction procedure	12	5
Legal abortion 2 step procedure	2	2
Legal abortion abdominal hysterotomy	1	0
Dilatation and curettage	10	1
Conization	4	0
Cervical rupture repair	2	0
Laparoscopy	1	2
Extirpation of ovarian cyst	2	0
Salpingectomy	1	0
Extirpation of condylomas	3	0
Total	42	16

timated by clinical examination and measurement of the bi parietal diameter by means of ultrasound For the ultra sound measurements a Brüel and Kjaer real time equipment with a revolving sector scan transducer of 2 MHz was used and the calculations were made using the methods described by Campbell & Newman (9) and Thompson *et al* (30)

Infants Thirty three liveborn babies were admitted to the neonatal ward either immediately after birth or during the first week afterwards Their medical histories were reviewed in retrospect All infants were preterm i e 36 weeks of gestational age or less as assessed by maternal history obstetric data and clinical examination

The diagnosis of sepsis was based on clinical signs and a positive blood culture

Chest X ray was performed on all babies with respiratory problems Fulfilment of the following criteria was required to establish a diagnosis of idiopathic respiratory distress syndrome (IRDS) tachypnoea retractions grunting in creasing right to left shunt (i e oxygen requirement during the first 24 h) and typical radiological picture Respiratory distress without increasing right to left shunt and not caused by other specific conditions is referred to here as transient tachypnoea

Birth weight and size were compared with those given in Swedish neonatal growth charts (29)

Perinatal mortality is defined as the total number of in fants who died *in utero* after 28 weeks of gestation or dur ing their first week of life irrespective of gestational age Autopsy was performed on all deceased infants

Statistical calculations If not otherwise stated the calcula tions were made in the following way fourfold tables were constructed on a pair basis for differences in qualitative

Table II *Complications in previous pregnancies*

	PROM	Controls
Bleeding	0	2
Toxaemia of pregnancy	5	2
Premature contractions	2	3
PROM	4	1
No complications	6/19	13/19

Table III *Complications during the pre[illegible] cy*

	PROM	C[illegible]
Bleeding 1st trimester	9	[illegible]
Bleeding 3rd trimester	3	1
Infections	5	[illegible]
Toxaemia of pregnancy	0	[illegible]
Polyhydramniosis	1	[illegible]
Premature contractions	6	[illegible]
No complications	10 30	[illegible]

variables and the hypothesis equal or [illegible] in the control group was tested against the [illegible] hypothesis higher frequencies in the observ[illegible] using the binomial (McNemar's) test (1).

RESULTS

Mothers

Frequency During the period 3 391 [illegible] delivered in the Department Th[illegible] PROM were admitted correspond[illegible] frequency of 0 9 per cent

Previous gynecological history Fertility [illegible] (primary or secondary involuntary steril[illegible] years) preceding the last pregnancy we[illegible] 23 per cent of the PROM patients as [illegible] 7 per cent among the controls the di[illegible] ing significant statistically however A[illegible] previous genital infections were not fo[illegible] represented among the PROM pa[illegible]

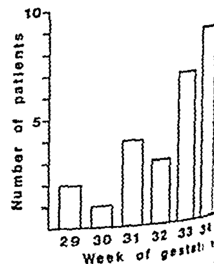
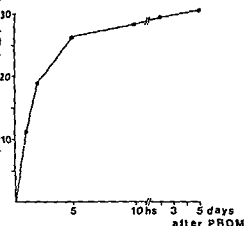


Fig 2 Time incidence of premature rupture [illegible] branes



3 Interval between premature rupture of the mem s and admission to hospital

ifferences in coital frequency in the two groups ne case only did PROM follow directly upon is

e distribution of previous genital operations is n in Table I These operations were found to be ficantly overrepresented (p=0 01) in the PROM p the number of patients with more than one ly cervical operation also being significantly r (p=0 05) As could be expected there was an increased frequency (p=0 02) of more ob- s cervical trauma such as conization and cervical are in the PROM material

ious obstetric history There was no over sentation of multiparous women in the material er cent of the patients being nulliparas or iparas The PROM patients had no increased ency of previous spontaneous abortions when pared with the controls Legal abortions on the r hand were found to be more frequent among PROM patients A 15/7 ratio does not however spond to statistical significance (Table I) The early versus late legal abortion did not differ ficantly in the two groups

omplications during previous pregnancies are l in Table II There was a higher incidence of tox a and PROM in the PROM group though not stically significant

nt pregnancy Complications during the present nancy are shown in Table III There was a higher ence of infections premature contractions and ding in the PROM pregnancies the last men d finding being the only one statistically signifi (p=0 01)

One case of acute enteritis preceding PROM was reported This was the only case of intercurrent disease with a possible direct relation to the PROM

Hard physical labor as a predisposing factor to PROM could not be verified 4 patients in each group stating that they had ardous occupations

The PROM group contained significantly more heavy smokers (>11 cigarettes/day) than the control group (p=0 01)

Obstetric outcome The time incidence of PROM ranged from 29 to 35 weeks (Fig 2) Two of the con trols were delivered in the 36th week of gestation in both cases however without any signs of PROM none of the other controls were preterm

The time interval between the PROM and admis sion to hospital is shown in Fig 3 The last 2 patients admitted arrived 2 and 5 days respectively after the PROM

In the PROM group there were 4 twin pregnancies and 26 singletons Among the latter there were 22 ver tex and 4 breech presentations (15 per cent) The ex pected breech frequency of about 3 per cent at term was found among the controls Twenty five patients were delivered vaginally and 5 by Caesarean section (16 7 per cent) The average frequency of Caesarean section in the Department during the same period was 8 7 per cent Altogether operative intervention was necessary in 8 cases due to imminent asphyxia (3) in fection (2) premature breech presentation (2) and transverse lie (1) The operations were Caesarean sec tion (5) vacuum extraction (1) and manual extraction (2) Fifty-eight per cent of the patients primarily in tended for conservative treatment subsequently need ed operative intervention as compared with 5 per cent among the actively treated subjects The dif ference reflects the fact that the latter group contain ed the more mature infants Of the 4 twin mothers 3 were delivered by Caesarean section and the fourth was delivered vaginally because of infection Three of the control patients (10 per cent) had a Caesarean sec *tion (indications feto-pelvic disproportion partial* abruptio of the placenta stillborn infant + steriliza tion) while the rest were delivered vaginally without complications

All placentas were sent for histopathological analysis The extent of calcification and infarction was about the same in the two groups amounting to about 15 per cent Three of the PROM patients (10 per cent) had a placenta with abnormal umbilical cord insertion one membranous and two marginal insertions No such anatomical variations were found

Table I *Previous genital operations*

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Legal abortion abdominal hysterotomy	1	0
Dilatation and curettage	10	1
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Laparoscopy	1	2
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Birth weight and size were compared with those given in Swedish neonatal growth charts (29)

Perinatal mortality is defined as the total number of infants who died *in utero* after 28 weeks of gestation or during their first week of life irrespective of gestational age Autopsy was performed on all deceased infants

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Table III *Complications during the pregnancy*

	PROM	Con[illegible]
Bleeding 1st trimester	9	
Bleeding 3rd trimester	3	1
Infections	5	
Toxaemia of pregnancy	0	1
Polyhydramniosis	1	1
Premature contractions	6	4
No complications	10/30	[illegible]

variables and the hypothesis equal [illegible] in the control group was tested against the [illegible] hypothesis higher frequencies in the [illegible] using the binomial (McNemar s) test (1)

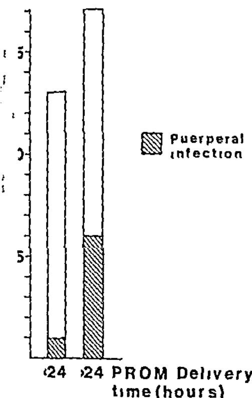
RESULTS

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Previous gynecological history [illegible] (primary or secondary involuntary [illegible] years) preceding the last pregnancy [illegible] 23 per cent of the PROM patients as [illegible] 7 per cent among the controls the differ[illegible]ing significant statistically however A[illegible] previous genital infections were not [illegible] represented among the PROM patients [illegible]

Fig 2 Time incidence of premature rupture [illegible] branes



ł Puerperal infection in relation to PROM delivery

ng the controls Only one of the vaginally ered PROM patients (4 per cent) had manual val of the placenta The average frequency of ype of intervention in the Department during the d was 1 5 per cent

peral infections A patient with clinical signs of al infection was considered puerperally infected body temperature measured ≥ 38 C on two oc nts separated by one hour or more All cases of peral and/or neonatal infection are listed in IV The incidence of puerperal infection in the M group was 27 per cent Patients with PROM ery time > 24 h developed puerperal infection in r cent of the cases as compared with 8 per cent patients with a PROM delivery time < 24 h the rence being statistically significant ($p < 0.05$ ter s exact test) Compared with the controls who no puerperal infections the PROM patients ered > 24 h after PROM had a significantly in ed incidence of puerperal infection ($p < 0.001$) relation between PROM delivery time and peral infection is illustrated by Fig 4 As could be expected the majority of puerperal infections occurred in patients with a PROM delivery time > 24 h No prophylactic antibiotics were used therapy being instituted only when clinical signs of amnionitis appeared All cases of puerperal infection reacted well to antibiotic therapy

Infants

The group of neonates studied consisted of 18 boys one stillborn 16 girls and included four sets of twins Birth weights varied between 950 and 2 730 g Two babies each a twin were small for date while 2 infants were large for date the rest being of a size appropriate for their gestational age Neonatal asphyxia (i e an Apgar score of 6 or less at 5 min) was recorded in 5/33 (15 per cent) newborn babies

IRDS was diagnosed in 3 (9 per cent) infants (Table IV) Two of these died each a twin Both infants received treatment with CPAP (continuous positive airway pressure via a nasal cannula) and later with respirator The twin sister of the latter died of intraventricular and pulmonary hemorrhage One of 3 infants with IRDS survived Fourteen (42 per cent) other babies had varying causes (transient tachypnoea 11 pneumothorax 1 Wilson Mikity 1 meconium aspiration 1) and degrees of respiratory distress and received oxygen therapy The outcome was favorable in these cases

Septicaemia was diagnosed in 4 babies (Table IV) and was suspected but not confirmed in 2 other infants

One aforementioned twin died of Klebsiella sepsis in connection with IRDS another of combined Klebsiella and group B streptococcal sepsis In the latter case the streptococcal pathogen was isolated from the mother s cervix as well and she also had clinical signs of puerperal infection

Three of the 4 confirmed cases of sepsis were found among infants with no longer than median (25 h) duration of PROM This distribution did not reach statistical significance however

Only one of the 4 mothers of infants who later had sepsis had an elevated body temperature (38° C or more) perinatally Another of these mothers later developed postoperative infection which necessitated a repeat laparotomy and abscess drainage In this case however the same microorganism could not be traced in both mother and child Maternal fever preceding delivery was encountered in 6 cases (Fig 5)

One infant with a birth weight of 950 g and a gestational age of 29 weeks died of asphyxia during a breech delivery In this case group B streptococci

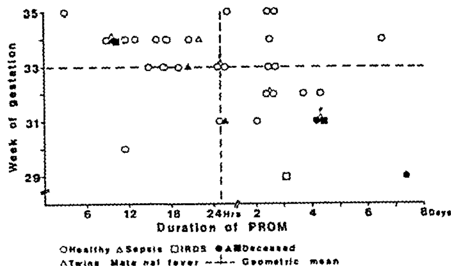


Fig 5 In [illegible]

were isolated from the mother s cervix and the amniotic fluid as well No culture was taken from the stillborn infant An infection of the urinary tract was diagnosed in one patient at 2 weeks of age

The total perinatal mortality was 6/34 (3 boys and 3 girls) or 17 6 per cent No other fatal disease occurred during the remainder of the neonatal period (28 days after birth) Fig 5 shows the occurrence of IRDS sepsis mortality and maternal fever in relation to the gestational age and duration of PROM

Infants delivered from the mothers in the control group had no neonatal infections and were all singletons

Congenital malformations One asymptomatic ventricular septum defect one congenital scoliosis with a hemivertebra and one chondrodystrophia were diagnosed among the PROM cases

Twin pregnancies In the PROM group there were four twin pregnancies (13 per cent) The controls were all singletons The four twin mothers all showed clinical signs of infection 3 of them 0 5 – 2 5 hours after PROM necessitating completion of the delivery the fourth mother having peritonitis after Caesarean section Three of the 8 twin infants died (37 per cent)

DISCUSSION

The varying *incidence* of PROM reported from 2 per cent to 32 6 per cent (2) reflects the fact that there is no generally accepted definition of the condition Commonly it is defined as rupture of the membranes prior to the onset of uterine contractions which thus also includes the full term cases Since full term cases usually do not constitute any obstetric or pediatric problems the present study was restricted to [illegible] cases occurring prior to the 36th week of [illegible] Thus the PROM incidence in this material [illegible] cent) should be viewed in this context

Several previous reports have dealt with the *effects of legal termination* on subsequent [illegible] cies (19 21 28 32) Koller & Eikhom (17) [illegible] significantly increased incidence of [illegible] ($p < 0.001$) in a subsequent pregnancy in [illegible] had their first pregnancy legally terminated [illegible] sociation could also be traced in our material [illegible] not statistically supported

The tendency of patients terminated [illegible] develop PROM and to deliver prematurely [illegible] quent pregnancies has been assumed to be [illegible] *cervical incompetence* caused by [illegible] time of operation (19 28) Johnstone et al measured the diameter of the internal cervical [illegible] patients previously operated by suction [illegible] and found significantly greater cervical [illegible] compared with controls In support of the [illegible] assumption we found a significantly higher [illegible] of patients with more than one cervical [illegible] the PROM group in comparison with the [illegible] ($p = 0.05$) and the same was true of the [illegible] cervical traumas following conization [illegible] rupture ($p = 0.02$) Johnstone et al (14) [illegible] mal cervical diameter in patients where the [illegible] did not exceed 10 mm whereas [illegible] measurements were encountered when the [illegible] had been more than 12 mm These [illegible] the possibility of more serious sequelae [illegible] as a result of late terminations [illegible] material however no significant difference [illegible] early and late legal abortions was found

rtility problems were found to be more frequent e PROM group This should probably be con ed a late complication of legal termination rather a primary condition

previously reported overrepresentation of *twin nancies* among PROM patients (22) could also be d in our study *Polyhydramnios* however was untered in one patient only Naeye *et al* (25) ted from a large prospective study that 11 per of the twin deaths were caused by PROM while erinatal mortality rate for twins was found to be times that for singletons In our material what corresponding relationships were observ vith a threefold increase in the mortality rate for Furthermore all the twin mothers became in d during the puerperium Considering the es found in our material and those of Naeye *et* 5) it should be emphasized that the combination in pregnancy and PROM is prognostically a very us condition

i association between PROM and a possible tion in the *tensile strength of the membranes* been investigated by several authors with ive results (20 26) Thus a higher stress ince was found in preterm membranes as com l with term specimens Furthermore Lavery & r (20) have shown that the stress tolerance of the branes decreases with advancing gestational age forming suitable conditions for rupture at term also demonstrated that the membrane thickness e the application of stress was very similar in and preterm cases and that in fact preterm mem s tolerated greater stress application than term branes Consequently they concluded that in of PROM despite a basically better stress ance the rupture of the membranes might be by some *local defect*

seems reasonable to assume that an anatomical tion of the membranes such as a *marginal cord tion* might constitute such a local defect Thus y *et al* (8) in 32 cases of marginal cord inser found a 65 per cent incidence of premature and a 47 per cent incidence of PROM These ors suggested that marginal insertion of the cord cause interference with adequate fetal circulation thereby restrict nutrition of the fetus and finally ute labor prematurely It is also conceivable that a oral or velamentous cord insertion engaging or less of the adjacent fetal membranes could them more friable by reducing their normal ance to s ress In our 30 PROM pregnancies we found 2 marginal and 1 membranous insertion cor responding to a 10 per cent incidence as compared with 6 per cent in the Brody material (8)

Secondarily acquired defects of the fetal mem branes as a result of *poor nutritional status* have been suggested by Wideman *et al* (31) They found a rela tionship between low plasma ascorbic acid levels and PROM in patients coming from lower socioeconomic classes Probably the low ascorbic acid levels in these patients reflect their generally poor nutritional status

Meyer *et al* (23) found another interesting rela tionship between *smoking* and PROM reporting a threefold increase in the risk of PROM for smokers among deliveries before the 34th week of gestation This finding was verified in our study where we found significantly ($p = 0\ 01$) more heavy smokers in the PROM group than among the controls

Almost 30 years ago Knox & Hoerner (17) were able to demonstrate degenerative changes at the site of rupture in membranes from patients delivered prematurely They assumed that these local defects of the membranes were caused by *ascending infection* which made them inflamed and friable They also suggested that the infection could result in an increas ed irritability of the uterus thus initiating contrac tions and finally PROM Their paper however did not include microbiological studies Since then many investigators have tried to elucidate the microbiologi cal flora in patients with PROM in order to reveal organisms responsible for this clinical condition and for the possibly occurring puerperal and neonatal in fections These attempts however have not adduced any indisputable experimental support for the theoretically attractive hypothesis of Knox & Hoerner On the other hand the significance of ascen ding infection for the maternal and especially the neonatal outcome has been well documented (2 4 7 12 13 24 27)

In clinical obstetrics an ominous sign of impending amnionitis following rupture of the membranes is the occurrence of *maternal fever* According to Bobitt *et al* (7) maternal fever could however often be a late sign of ascending infection In their material they frequently encountered microbiological evidence of amnionitis without any maternal fever In our study we found maternal fever to be an unreliable prognostic indicator The clinical course for the 6 mothers with fever was uncomplicated and only one of the 4 cases of neonatal sepsis came from this group

In the microbiological part of this study (12) we

have suggested that the significance of *anaerobic bacteria* in puerperal infections is probably greater than has earlier been realized Thus the total number of anaerobic isolates from the cervix outnumbered the aerobic ones both in the PROM group and among the controls It should be emphasized that we were able to isolate the generally pathogenic *Bacteroides fragilis* from the cervix amniotic fluid or placenta in 23 per cent of the PROM patients but not in a single case among the controls No correlation between these findings and the occurrence of puerperal infection could be established in this material however The findings of Del Bene *et al* (11) of a decrease and increase in the number of aerobic and anaerobic strains respectively on comparing patients with PROM after < 12 versus > 12 hours also suggest the importance of the role of anaerobes for the subsequent clinical course Further investigations to elucidate the significance of the anaerobes as causative or complicating agents are in progress

The significance of the *interval between PROM and delivery* has been a matter of endless discussion As is the case in this as well as in previous studies (2 13 24) the risk of puerperal infection increases with the length of the latent period Although in our material the majority of puerperal infections followed a favorable course there are reports of severe complications and even maternal deaths (4) which call for attempts to shorten the latent period On the other hand it is also necessary to take into consideration the neonatal risks caused by prematurity An active policy favors the outcome in terms of maternal and neonatal infection (2) On the other hand there are reports suggesting a lower incidence of IRDS after prolonged rupture of the membranes (3 6 24) which could possibly speak in favor of a conservative routine in selected cases The low incidence of IRDS in our present material does not allow of any conclusions as to the association of PROM with a reduced frequency of IRDS Earlier as well as recently published studies present contradictory results leaving the issue open to debate (2 3 6 15 24)

In the present material there was a high perinatal mortality (17 6 per cent) Mortality rates between 4 1 and 20 per cent are found in comparable studies (2 6 10 13) The present relatively high mortality rate should be considered in the light of the fact that all the neonates lost had low birth weights between 950 and 1 950 g (mean 1 335 g) A correspondingly high mortality rate for infants in the 1 000 – 2 500 gram range (15 1 per cent) has been reported by [illegible] (13) The overall morbidity in th[illegible] ly high only 9/33 infants (27 per cent) [illegible] uneventful neonatal period not requir[illegible] incubator care and phototherapy Pryle[illegible] reported an 8 per cent and Knudsen et al (1[illegible] cent incidence of proven septicaemia [illegible] prematures born after PROM as compared [illegible] per cent in the present material No [illegible] tion was found between neonatal sepsis and [illegible] ed rupture of the membranes in the present [illegible]

It should be mentioned that in 3 out of 4 [illegible] neonatal sepsis the etiological agent had already [illegible] isolated from nasal swabs taken from the [illegible] mediately after delivery (12) which allowed [illegible] stitution of early therapy

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Acta Obstet Gynecol Scand 59 395–404 1980

AUDITORY EVOKED RESPONSES OF THE HUMAN FETUS

I Behavior during progress of labor

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ly studies demonstrate that the human fetus can and react to auditory stimulation during preg y (1 5 6 8 10 12 14 15 20) Modifications of reaction during labor have been described by etta (20) Barden (1) Hon (10) and Rosen (16 18 19) have shown that this behavior involves eption of stimuli resulting in an increase in the ncal activity of the fetal brain and that modifi ons of these patterns are elicited by several stimuli by labor trauma Hon (10) Garcia Aust (7) and n (18) have attempted to correlate electroenceph raphic with fetal heart rate changes

hese studies suggest that auditory stimulation and valuation of the fetal responses offer a new ap ich to the investigation of at least one function of l brain during pregnancy and labor The ap- ich has the advantages of being harmless pro- ig an immediate result and needing unsophisti d instrumentation There is a lack of consistency te published reports probably caused by differ s in the type and intensity of the stimulus present the fetus This was confirmed by our early ex nce (13) It seemed logical to us that a suitable ulus applied with a consistent technique should l comparable responses Using this method we able to discriminate between the responses of ses in a favorable environment those in an un rable environment and those stimulated by labor

Similar results have been obtained by Read and er (15) who used a related procedure for in gating fetal condition in high risk pregnancies y based their conclusions on the absence or ence of fetal heart rate acceleration We use ral other parameters of the fetal heart rate onse and find that these provide fuller informa on fetal condition following a sound stimulus have termed this procedure the *Auditory evoked* onse

This paper deals with our observations of the auditory evoked response during labor The data came from a series of 180 unselected pregnant women whose labor was monitored electronically This paper is divided into two parts The first describes the modi fications observed in the auditorily evoked response with progress of labor The second part deals with several factors which influence the pattern of the fetal response In both studies the fetuses were divided in to those who were vigorous at birth (Apgar score 7–10) and those who were born in a depressed condition (Apgar score 1–6) These groups will be called vigor *ous and depressed fetuses respectively We plan to in* vestigate the children psychologically to ascertain any possible significance of the variations observed in the auditory evoked response and to try to correlate this new test of cerebral function in the fetus with post natal mental development and behavior

MATERIAL

Sound stimulation was delivered to the fetus through the maternal abdomen by a modified two-inch flat tweeter The frequency used was 1 500 cycles per second and the out put was 125 decibels (measured at the driver s surface) The stimulus was generated by a specially built oscillator ampli fier which provided 5 pulses lasting 2 seconds each separated by one second intervals During the procedure fe

Table I *Motor responses (all stimuli)*

	Response			
Newborn	Absent	Mild	Intense	
Depressed	19	27	17	63
Vigorous	42	138	133	313
	61	165	150	376

$x^2 = 12.24$ with two degrees of freedom $p < 0.01$

Table II *Motor responses and progress of labor in the group of vigorous newborns*

Motor response	Cervical dilatation in cm 1–3	4–7	8–10	
Absent	7	11	24	42
Mild	35	56	47	138
Intense	31	64	38	133
	73	131	109	313

$\chi^2 = 12.33$ with 4 degrees of freedom $p<0.07$

Table III *Motor responses and progress of labor in the group of depressed newborns.*

Motor response	Cervical dilatation in cm 1–3	4–7	8–10	
Absent	3	8	[illegible]	[illegible]
Mild	10	8	[illegible]	[illegible]
Intense	7	7	3	[illegible]
	[illegible]	23	20	[illegible]

$\chi^2 = 4.58$ with 4 degrees of freedom (not significant)

tal heart rate and uterine contractions were monitored by a suitable fetal monitor (H P 8030 A Corometrics 101 or 111 B) modified to record the pulses of sound stimuli Only patients in active labor were used for this study which was undertaken between November 2nd 1974 and December 27th 1977 One hundred and eighty cases from the private practice of two of the authors were studied the only criteria for selection being the availability of the apparatus and of the personnel involved in this research This group contained many high risk patients We tried to apply not less than three sets of stimuli to each case at 1–3 cm at 4–7 and after 8 cm of cervical dilatation This was not always possible because of clinical conditions A total of 376 sound stimuli were applied with a mean of 2 09 sets of stimuli per case

METHODS

In the interpretation of fetal responses to sound stimuli, we have evaluated the
1) motor responses
2) heart rate responses

1) Motor responses Sound stimulation as described [illegible] always produced an active motor response from the [illegible] normal pregnancy (NPL 13) and in 8[illegible] per cent of the fetuses studied during labor (Table I) This motor [illegible] consists primarily of strong and sudden fetal movements similar to a Moro reflex in the newborn This is followed by a definite increase in fetal activity which [illegible] for 30 minutes or more This reaction is associated with the fetal heart rate response but lasts longer The [illegible] movements coincide with transient fetal heart rate [illegible]

Table IV *Comparison of measured values between the groups of vigorous/depressed newborns* [illegible]

Measured value	Vigorous newborns	Difference	Depressed newborns
Duration of fetal heart rate response			
Sec	223 71		[illegible]
S E	11 93		[illegible]
Number	308		43
Difference t value		5 51	
Difference significance		$p<0.000001$	
Difference between mean values of FHR before and after stimulation			
Beats/min	9 86		[illegible]
S E	0 72		[illegible]
Number	144		45
Difference t value		3 81	
Difference significance		$p<0.001$	
Initial increase in fetal heart rate			
Beats/min	20 98		[illegible]
S E	0 74		[illegible]
Number	309		44
Difference t value		4 33	
Difference significance		$p<0.0001$	
Maximal increase in fetal heart rate			
Beats/min	28 91		[illegible]
S E	0 92		[illegible]
Number	283		44
Difference t value		5 31	
Difference significance		$p<0.000001$	

ɔle V *Measured values of FCF and progress of labor in vigorous newborns*

ısured values	Cervical dilatation 1–3 cm	Diff	Cervical dilatation 4–7 cm	Diff	Cervical dilatation 8–10 cm
ration of fetal heart rate response					
ec mean	295 93		230 71		167 45
D	231 65		181 92		211 62
.E.	27 30		16 21		20 36
lumber	72		126		108
ıfference significance		$p<0.05$		$p<0.02$	
			$p<0.001$		
f between mean values of FHR before and after stim					
eats/min mean	12 67		8 36		6 68
D	7 15		8 64		9 04
E	1 26		1 01		1 35
umber	32		73		45
ıfference significance		$p<0.01$		n s	
			$p<0.002$		
al increase in fetal heart rate					
eats/min mean	24 07		22 54		17 74
D	12 64		12 31		13.29
E	1 50		1 12		1 27
umber	70		117		97
ifference significance		n s		$p<0.01$	
			$p<0.01$		
increase in fetal heart rate					
eats/min mean	32 33		28 63		25 82
D	13 32		15 81		16 44
E	1 59		1 46		1 67
umber	70		117		97
ifference significance		n s		n s	
			$p<0.01$		

s, which continue even when the basal fetal heart rate returned to pre stimulation values The intensity of the or response varies from case to case so that a simple ification of present/absent seemed insufficient The ification of the intensity of the motor response was ribed in the previous publication and has been used in this study It is as follows

se motor response a strong sudden generalized move of the fetus easily recognized by the observer or felt he mother usually followed by a prolonged period of ased fetal activity

motor response a movement felt by the mother or rved by the attendant which could be sudden but was strong usually not followed by any detectable increase tal activity

nt motor response no movement detected by the rver or felt by the mother

eart rate responses The fetal heart rate changes were ied by direct reading of the records from the fetal moni The following items were measured *duration of fetal t rate acceleration differences between means initial ase of fetal heart rate* and *maximal increase of fetal t rate*

ation of fetal heart rate acceleration We always obtain acceleration response (Fig 1) when the fetus was not ely depressed The duration of the response was meas- on the record in mm from the beginning of the stimulation to the point where the fetal heart rate returned to the pre-stimulation level for a steady period of not less than 5 mm (30 seconds) The measured values have been converted into time in seconds to facilitate the calculations

Differences between means The basal fetal heart rate was determined for at least five minutes before stimulation by taking the mean of the values at each peak on the fetal heart rate tracing The same procedure was continued for the period of acceleration following stimulation and the values obtained were compared statistically using Student s test for dependent samples

Initial increase of fetal heart rate This was the difference between the fetal heart rate immediately preceding stimulation and the first peak on the record after stimulation The strong movements of a vigorous fetus sometimes hamper the analysis of this parameter when the fetal heart rate is monitored by external ultrasound techniques

Maximal increase of fetal heart rate This was the difference between the greatest value attained by the fetal heart rate during the period of acceleration and the value immediately before stimulation

Besides these responses we have occasionally observed a sudden deceleration of fetal heart rate at the beginning of the response this was sometimes associated with entanglement of the cord around the fetal neck This finding was too infrequent to warrant detailed analysis The same applies to the increased frequency of transient accelerations observed after sound stimulation Such accelerations are additional

Table VI *Measured values of FCF and progress of labor in depressed newborns*

Measured values	Cervical dilatation 1–3 cm	Diff	Cervical dilatation 4–7 cm	Diff	[illegible]
Duration of fetal heart rate response					
Sec	167 21		129 78		[illegible]
S D	160 62		112 56		[illegible]
S E	36 85		23 47		[illegible]
Number	19		23		[illegible]
Difference significance		n s		p<0.0[illegible]	
			p < 0 01		
Diff between mean values of FHR before and after stim					
Beats/min	7 19		6 86		[illegible]
S D	8 90		6 39		[illegible]
S E	2 16		1.36		[illegible]
Number	17		22		[illegible]
Difference significance		n s		p < 0 01	
			p < 0 04		
Initial increase in fetal heart rate					
Beats/min	17 55		15 91		[illegible]
S D	12 01		10 76		[illegible]
S E	2 68		2.24		[illegible]
Number	20		23		[illegible]
Difference significance		n s		n.s.	
			p < 0 03		
Maximal increase in fetal heart rate					
Beats/min	23 53		21 04		[illegible]
S D	15 79		14 10		[illegible]
S E	3 62		2 94		[illegible]
Number	19		23		[illegible]
Difference significance		n s		p < 0 03	
			p < 0 0[illegible]		

evidence of fetal wellbeing but during labor they can be caused by many other factors so that numerical analysis is not possible

RESULTS

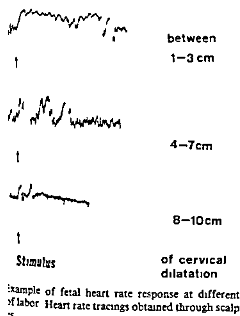
Motor responses We have analyzed 376 stimuli of which 313 were applied to the group of 151 vigorous fetuses and 63 to the group of 29 depressed fetuses Table I shows that the proportion of absent responses was greater in the group of depressed fetuses than in the group of vigorous fetuses A Chi square test indicated that the differences were significant at a level of $p<0.01$

We investigated whether the progress of labor could influence the pattern of the motor response For this we compared the data for each group (vigorous or depressed) with the degree of cervical dilatation (Tables II and III) The number of absent responses increased with the progress of labor in the group of vigorous fetuses A Chi square test was significant at $p<0.02$ No such trend was found in the group of depressed fetuses (Chi square not significant)

Heart rate responses With the kind of [illegible] a fetal heart rate response can always be [illegible] was observed in normal or mildly depressed [illegible] (Fig 1) This agrees with our previous observ[illegible] labor (NPL 13) The response obtained [illegible] and clearly delineated in all cases where the [illegible] not agitated or actively moving It consists [illegible] acceleration beginning immediately after [illegible] tion bringing the basal heart rate to a level [illegible] the previous rate This is maintained for [illegible] less than 200 seconds after which the [illegible] falls back to the previous level Sometimes [illegible] *the response is marked by an* abrupt fall [illegible] ition from the steady elevated rate to a [illegible] closely associated transient accelerations [illegible] heart rate response is considered ter[illegible] period between each accelera[illegible] more of a steady rate equal to or only [illegible] the previous level It was possible to measure [illegible] ference between the mean values of the [illegible] rate before and after stimulation in [illegible] the patients

ɔle VII *Differences in measured values between the groups vigorous/depressed newborns (numbers within entheses) during progress of labor*

	Duration of F H R response sec		Diff between means beats/min		Init increase in F H R response beats/min		Max increase in F H R response beats/min	
	Vig n b	Depr n b	Vig n b	Depr n b	Vig n b	Depr n b	Vig n b	Depr n b
vical dilatation 1–3 cm	295 93 (72)	167.21 (19)	12 67 (37)	7 19 (37)	24 07 (71)	17.55 (20)	32 33 (70)	23.53 (19)
diff t value	2 81		2 19		2 12		2 22	
diff significance	p<0 01		p<0 04		p<0 04		p<0 03	
vical dilatation 4–7 cm	‿30 71 (126)	129 78 (23)	8 36 (73)	6 86 (22)	22 54 (121)	15 91 (23)	28 63 (117)	21 04 (23)
diff t value	3 54		0 88		2 64		2 31	
diff significance	p<0 001		n s		p<0 01		p<0 03	
vical dilatation 8–10 cm	167 45 (108)	58 91 (22)	6 68 (45)	2 22 (21)	17 74 (109)	10 14 (21)	25 82 (97)	12.29 (21)
diff t value	4 25		2 94		3 43		4 70	
diff significance	p<0 0001		p<0 01		p<0 001		p<0 00001	



Example of fetal heart rate response at different of labor Heart rate tracings obtained through scalp s

A COMPARISON BETWEEN GROUPS OF VIGOROUS AND DEPRESSED FETUSES

Duration of the response The mean duration of the fetal heart rate response in the group of vigorous fetuses was 223 73 seconds In the group of depressed fetuses the mean was 116 68 seconds (Student s test gave p<0 0000001) (Table IV) Even considering the great variability in the data this parameter is very useful when predicting the condition of the neonate at birth (Fig 2)

Differences between means The results differed between vigorous and depressed fetuses In the former group the mean increase of fetal heart rate after sound stimulation was 9 86 beats per minute while in the group of depressed fetuses it was only 5 58 beats per minute Student s test gave p<0 001 (Fig 3)

Initial increase of fetal heart rate The initial increase of fetal heart rate in the group of vigorous fetuses amounted to a mean of 20 98 beats per minute while in the group of depressed fetuses it was 14 39 beats per minute Student s test gave p<0 0001 (Fig 4)

Maximal increase of fetal heart rate The greatest increase in fetal heart rate after sound stimulation

'III *Comparison of measured values at the end of labor in vigorous newborns and at beginning of labor essed newborns*

	Vigorous newborns at 8–10 cm of cervical dilatation	Depressed newborns at 1–3 cm of cervical dilatation
n of F H R response sec	167 45	167.26
tween mean values of FHR before and after stim beats/min	6 68	7 19
icrease in FHR beats/min	17 74	17 55
l increase in FHR beats/min	25 82	23.53

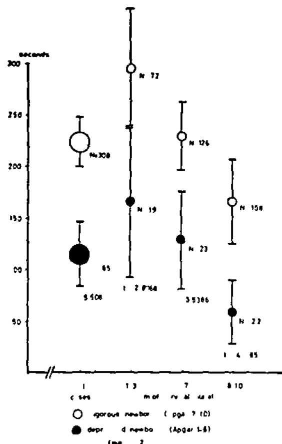


Fig 2 Length of fetal heart rate responses in vigorous and in depressed newborns (larger circles all cases smaller circles are values at different periods of labor

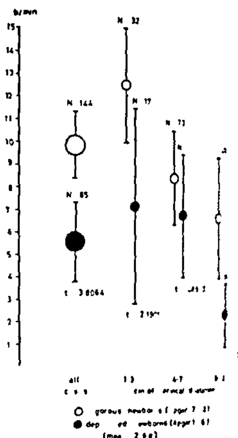


Fig 3 Differences between means in vigorous an_ fetuses (larger circles all cases sma_er circles are at different periods of labor)

amounted to a mean of 28 91 beats per minute in the group of vigorous fetuses and 18 32 beats per minute in the group of depressed fetuses Student s test gave p<0 000001 (Fig 5)

Comments The groups of vigorous and depressed fetuses differed significantly in all the parameters measured The most discriminating function was the duration of the fetal heart rate response These observations suggest that fetal reaction to sound stimulation can be used during labor to identify the depressed fetus The decrease in fetal heart rate response usually precedes other signs of fetal depression and is sometimes the only available predictor of neonatal depression

B DIFFERENCES DURING PROGRESS OF LABOR

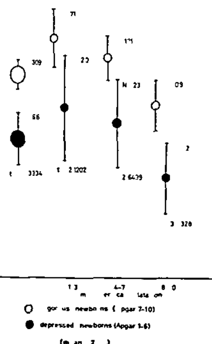
The results were also analyzed within the groups of vigorous and depressed fetuses These data are shown in Figs 2–5 and in Tables V – VIII

Vigorous fetuses (Table V)

Duration of fetal heart rate response T_ the fetal heart rate response decreased signi_ labor progressed The values were 295 91 sec_ 1–3 cms 230 71 seconds at 4–7 cms an_ sec_ onds at 8–10 cms of cervical dila_tion. T_ ences between these values were all sta_ _icant It is interesting that the mean at 8_ cervical dilatation in this group of vigoro_ equal to the mean observed at the beginni_ in the group of depressed fetuses (Fig 2)

Differences between means The differen_ means before or after sound stimula_ _ labor progressed The values were 12 5_ 6 68 beats per minute for the succes_ cervical dilatation Significant differences _ between the means at 1–3 and 4–7 cms (_ p<-0 01) and between those at 1–3 and _ (t=3 2411 p<0 002) (Fig 3)

*Initial increase of fetal heart r_* The_ decreased with progress of labor The ext_



Initial increase of fe tal heart rate in vigorous and de
d fetuses (larger circles all cases smaller circles are
at different periods of labor)

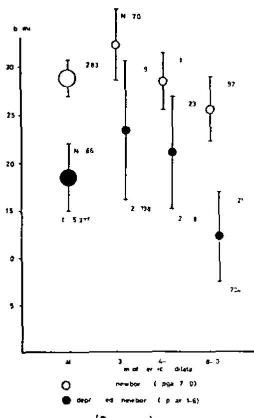


Fig 5 Maximal increase of fetal heart rate in vigorous and depressed fetuses (larger circles all cases smaller circles are values at different periods of labor)

stages were 24 07 22 54 and 17 74 beats per
te Statistically significant differences were
d between the means at 1–3 and 8–10 cm
2178 p<0 01) and between those at 4–7 and
0 cm (t=2 8315 p<0 01) (Fig 4)
imal increase of fetal heart rate This measure
of fetal heart rate response fell steadily as labor
ressed but not as markedly as the other parame
neasured A significant difference was found on
tween the values at 1–3 and 8–10 cm of cervical
ation (t=2 8227 p<0 01) (Fig 5)

ressed fetuses
ation of fetal heart rate response The fetuses that
born depressed had a shorter duration of fetal
t response in early labor compared with those
vigorous and also showed a more marked de
e in the response as labor progressed At the be
ing of labor the response lasted 167 21 seconds
l to 129 78 at 4–7 cm of cervical dilatation and
91 seconds at 8–10 cm The latter amounts to only 35 23 per cent of the initial response while in the group of vigorous fetuses the response at the end of labor was 56 58 per cent of the initial response Significant differences were observed between 1–3 and 8–10 cm (t=2 7110 p<0 01) and between 4–7 and 8–10 cm (t=2 1915 p<0 04) (Fig 2)

Differences between means Similar trends were observed for this measurement of the fetal heart rate response the values being 7 19 6 86 and 2 22 beats per minute Despite a great range and the relatively small number of cases studied significant differences were found between the means at 1–3 and 8–10 cm (t=2 1915 p<0 04) and between those at 4–7 and 8–10 cm (t=3 0352 p<0 01) (Fig 3)

Initial increase of fetal heart rate The same progressively decreasing pattern of response intensity was observed for this function The mean values were 17 55 15 91 and 10 14 beats per minute at the three periods of labor studied A significant difference was observed only between 1–3 and 8–10 cm of cervical dilatation (t=2 2801 p<0 03) (Fig 4)



Fig 6 Example of fetal heart rate acceleration elicited by touching cephalic presentation in absence of heart rate response to sound stimulation

Maximal increase of fetal heart rate The mean values for this function also diminished with progress of labor They were 23 53 21 04 and 12 29 beats per minute for the periods of labor considered Significant differences were observed between 1 – 3 and 8 – 10 cm ($t = 2\ 6054$ $p < 0\ 02$) and between 4 – 7 and 8 – 10 cm of cervical dilatation ($t = 2\ 3279$ $p < 0\ 03$) (Fig 5)

C DIFFERENCES BETWEEN THE GROUPS OF VIGOROUS/DEPRESSED FETUSES DURING PROGRESS OF LABOR

There were statistically significant differences between the groups of vigorous and depressed fetuses for all the parameters studied A comparison was made between the mean values of each measurement for the groups of vigorous and depressed fetuses at each period of labor

Duration of the fetal heart rate response The differences between the groups were 128 72 beats at 1 – 3 cm 100 93 beats at 4 – 7 cm and 108 54 beats at 8 – 10 cm of cervical dilatation All these differences were statistically significant ($t = 2\ 8068$ $p < 0\ 01$ at 1 – 3 cm $t = 3\ 5386$ $p < 0\ 001$ at 4 – 7 cm and $t = 4\ 2485$ $p < 0\ 0001$ at 8 – 10 cm) Although the numerical differences do not become larger with the progress of labor their significance increases

Differences between means The inter group differences were 5 48 1 5 and 4 46 beats at the three stages of dilatation Although this is not the best parameter for differentiating the vigorous from the depressed fetuses significant differences were observed at 1 – 3 cm and at 8 – 10 cm ($t = 2\ 190$ $p < 0\ 04$ and $t = 2\ 9425$ $p < 0\ 01$ respectively)

Initial increase of the fet l heart rate The [illegible] between vigorous and depressed fe[illegible] 6 63 and 7 6 beats per min [illegible] 2 1202 $p < 0\ 04$ $t = 2\ 6438$ $p < 0\ 01$ [illegible] $p < 0\ 001$) at the three stages of labor

Maximal increase of fetal heart rate Sig[illegible]ferences were observed between [illegible]sed fetuses At 1 – 3 cm the d fference [illegible] ($t = 2\ 2238$ $p < 0\ 03$) at 4 – 7 cm 7.9 [illegible] 2 3118 $p < 0\ 03$) and at 8 – 10 cm 13.9 [illegible] 4 7047 $p < 0\ 0001$)

DISCUSSION

The assessment of damage suffered by the fetus during labor or from [illegible] nancy is one of the problems of mod[illegible] The most important organ at risk the [illegible] difficult to investigate Electroenceph[illegible]ings of human fetuses have been obtained [illegible] related with fetal brain damage (7) [illegible] is complex and impracticable ex[illegible]

It is known that a sound stim[illegible] electrical activity in the fetal bra[illegible] studies in the fetus in the newborn [illegible] show that this is followed by a heart ra[illegible] Brazelton (4) has shown the behavi[illegible] external stimuli provide a most sen[illegible] evaluate the central and peripheral ne[illegible] of human infants Probably th s is also [illegible] fetus The study of this fetal a[illegible]

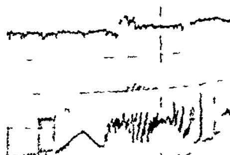


Fig 7 Fetal heart rate accelera[illegible] crease of intra abdominal press[illegible] ing when no response was obta[illegible] (Both examples from same case of [illegible] born Apgar 4/10 wi hout detecta[illegible]

use is a useful approach to the study of fetal con
on before birth

i the analysis of data presented in this paper
e facts need discussing The first is the decrease in
auditory evoked response with the progress of
l labor This occurs even when the fetus is go-
to be born vigorous and apparently normal and
ests that some kind of change in cerebral func
occurs even under physiological conditions This
ease of the auditory evoked response is also pre
in many conditions where fetal depression is
wn to occur such as in cases of cephalo-pelvic
ion premature rupture of the membranes
small for-dates syndrome and in preeclampsia
and others have previously described the absence
ny response when the fetus is seriously depressed
15) A careful follow up of the present infants
help to clarify the meaning of these observations

econdly it seems that the fetal auditory evoked
onse involves a sensitive parameter of fetal brain
ity In cases of mild fetal depression where no
response can be obtained a response in the form
etal heart rate acceleration and fetal movement
still be elicited by other external stimuli such as
rnal vomiting touching the fetal presentation
This is demonstrated in Figs 6 and 7

nother point to be considered is the differences
rved in the development of the motor auditory
ed response in vigorous compared with depress-
etuses With vigorous fetuses the response de
ses with the progress of labor while with depres-
etuses the response is already decreased at the be
ing of labor and does not change with progress of
ation This suggests that the mechanisms produc
he fetal heart rate and the motor responses are
ively independent as they behave dissimilarly in
group

final point to be stressed here is that the depres
of the fetal auditory evoked response can pre
other signs of fetal distress An impaired res-
e can sometimes be identified during pregnancy
the beginning of labor The response of the fetus
oustic stimulation may provide a new and rela
y simple way of assessing the condition of the fe
rain The following points are important

etal monitors are available in the majority of
ell-equipped hospitals

ound stimulators are easy and cheap to build or
dapt

he perception and response to sound stimulation
functions of cerebral cortex as already dem
onstrated by fetal or neonatal electroencephalograms

4) the human fetus has been demonstrated to hear from 24 weeks of pregnancy a period of gestation when a poor intrauterine environment may begin to affect its development (12)
5) the fetal heart rate and motor responses are parameters of fetal condition
6) the method can be used during pregnancy since the procedure is non invasive
7) the test can be repeated several times since it causes no harm to the mother and is much less time-consuming than the oxytocin challenge (Pose test) or similar procedures
8) at the frequency used the attenuation of noise by the maternal abdomen ensures that no harm will result to auditory organs of the fetus since the noise reaching the amniotic fluid is several decibels below the normal sound levels in the intra uterine environment (21)

We have termed this test auditory evoked response in spite of the fact that the term evoked response is more often associated with electroencephalography This nomenclature was used in our introductory paper on the subject (14) The behavior of the auditory evoked response during complications of labor will be presented in part two of this paper A third paper will deal with this new test during pregnancy relating it to the oxytocin challenge (Pose test) and to the outcome of pregnancy

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CLINICAL AND ULTRASONIC ASPECTS IN THE DIAGNOSIS AND FOLLOW UP OF PATIENTS WITH EARLY PREGNANCY FAILURE

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...act The value of some central clinical and ultrasonic ...igs at the time of threatened abortion was examined in ...atients in the 6th–20th weeks The outcome of the ...ancy was delivery in 45 per cent of all the cases A ...ion of the first bleeding of 3 days or more predicted ...ion significantly more often than did a shorter ...ing episode A positive detection of fetal life signs by ...ound signified a successful outcome for the pregnancy ... per cent of the patients The anamnestic duration of ...ancy often seemed to deviate from the real weeks re...ng correction by ultrasonic methods Forty-eight per ...of the cases with various pathologic forms of early ...ancy were evacuated on the basis of ultrasonic fin... without waiting for the unavoidable spontaneous ...ion The later course of the pregnancies with a suc...l outcome revealed an 8 per cent frequency of ...ture deliveries signifying careful observation of the ...ts in this respect The relatively high frequency of ...tal mortality (3 4 per cent) seemed to be associated ...the prematurity

...symptoms of early pregnancy failure — uterine ...ing and contractions — constitute a very com... diagnostic problem during pregnancy The most ...rtant matters to be settled in this connection are ...y the confirmation of pregnancy secondly its ...ion and thirdly specification of the prognostic ...a for the outcome of the pregnancy Since ...60 per cent of these pregnancies will end in spon...ous abortion (7 8) and the frequency of ...mosomal anomalies in the abortive tissues is ...t 60 per cent (12) an early and reliable differen... diagnosis between normal and pathologic ...nancies is very important Only after this dif...tiation can the controlling and possible ...peutic measures be applied to the cases in which ...rmal outcome of the pregnancies can be ex...d

...ring the last ten years the ultrasonic methods ... attained a central role in the diagnosis of pro...s in early pregnancy The detection of the gesta... sac in the uterus from the 6th week onwards (4) the reliable diagnosis of fetal life signs in the 8th–10th week (9 15 17) and the differentiation of the pathologic forms of early pregnancy from the normal ones (20) which have been rendered possible by these methods have opened up entirely new possibilities for the clinician in solving the problems considered here After that the main task is to predict the subsequent prognosis of the pregnancy The first observations seemed to signify a successful prognosis for 90 per cent of the pregnancies after threatened abortion if the fetal life signs can be detected (9 10) In the older reports the chief perinatal complications (increased perinatal mortality prematurity and con genital malformations) seemed to occur significantly more often in pregnancies complicated with threaten ed abortion than in control pregnancies (2 11 21) Later observations however have only confirmed the increased frequency of prematurity establishing the other pathologic parameters as secondary conse quences due to the premature delivery (13)

The aim of this study is to present some central clinical and ultrasonic aspects of the actual diagnostics of early pregnancy failure and some follow up observations until the termination of pregnancy

MATERIAL AND METHODS

The series consisted of 525 patients admitted to the Depart ment of Obstetrics and Gynecology University of Oulu during about 4 years from 1973 onwards All the patients had uterine bleeding in the 6th–20th week of pregnancy The cases where the bleeding seemed to originate from cer vical polyps or erosion and no hormonal or histopathological verification of pregnancy could be made were excluded The series included 7 ectopic and 4 molar pregnancies All the cases were followed up until abortion or delivery Twelve per cent of the cases were outpatients while the others were followed up in the hospital The treat ment included only bed rest and symptomatic drugs

After the recording of anamnestic data and the clinical examination an ultrasonic examination (by one person) was

Table I *Ultrasonic findings at the first examination*

	Detection of fetal life	Empty gestation sac	Indistinct intrauterine echoes no gestation sac or fetus	Fetal echoes in gestation sac or in uterus, no signs of life	[illegible]	[illegible]
Number	202	142	92	75	4	[illegible]
Percent	38	26	18	14	1	1

performed on all the patients within the first two days after admission Therefore the cases with immediate spontaneous abortion were mainly excluded The main purpose of the ultrasonic examination was to detect the fetal life signs by combining the A Doppler and TM methods with B scanning (Kretz Combison 200) Real time equipment (Vidoson) was also used on some patients The examination was repeated once in 154 cases and twice in 71 cases This was done mainly because of anamnestic uncertainty or clinical discrepancy concerning the duration of pregnancy or to confirm an initially negative finding The duration of pregnancy was checked by measuring the mean diameter of the gestation sac and/or the biparietal diameter of the fetus

The statistical analyses were made using Student s t test

RESULTS

The mean duration of pregnancy was 10 7±3 2 weeks at the beginning of the bleeding and 11 5±0 8 weeks at the first ultrasonic examination The mean duration of bleeding before the first examination was 4 0±5 5 days For 75 per cent of the patients followed up in the hospital the treatment was continued for 1–7 days

Thirty two per cent of the cases had one or more spontaneous abortions in their anamnesis and 7 per cent had had legal induced abortions For 45 per cent (233 cases) that pregnancy was the first

As regards anamnestic data the main interest was directed to the time of beginning and the duration of the first bleeding episode If this occurred within weeks 5–9 the outcome was abortion in 51 per cent the corresponding figure for the 10th–14th weeks being 53 per cent and that for the 1[illegible]–2[illegible] [illegible] 69 per cent These differences [illegible] statistically significant If the duration of [illegible] bleeding episode was 1–2 days the [illegible] abortion in 47 per cent compared [illegible] it was 3 days or more This difference [illegible] significant ($p<0.05$) A history of [illegible] taneous or legal abortions had no significant [illegible] the outcome of the pregnancy compared [illegible] other patients

The ultrasonic findings at the first examination [illegible] presented in Table I Fetal life was detected [illegible] tients (38 per cent) An empty gestation [illegible] typical finding of a blighted ovum was [illegible] 26 per cent Indistinct intrauterine echoes [illegible] gestation sac or a fetus representing [illegible] abortion were detected in 18 per cent of the [illegible] Fetal echoes without the diagnosis of life [illegible] ed abortion) were seen in 14 per cent

The final outcome in the whole series was [illegible] in 45 per cent (Table II) When fetal life [illegible] detected at one of the ultrasonic examinations [illegible] patients) the pregnancy ended in delivery in [illegible] (87 per cent)

Table II *The outcome of pregnancies after threatened abortion*

	Delivery	Spontaneous abortion	Ectopic pregnancy	Hydatidiform mole
No	236	278	7	4
%	45	52		1

Weight of baby >600 g

Table III *Correlation between fetal life [illegible] the first ultrasonic examination [illegible] the pregnancy*

Weeks of pregnancy	Detection of fetal life			[illegible]		
	No	Delivery	Abortion	[illegible]	[illegible]	[illegible]
6th	0	0	0	5	[illegible]	[illegible]
7th	2	40	40	[illegible]	4	[illegible]
8th	10	100	0	[illegible]	[illegible]	[illegible]
9th	24	90	10	[illegible]	[illegible]	[illegible]
10th	33	87	13	[illegible]	14	[illegible]
11th	37	93	7	51	[illegible]	[illegible]
12th	20	90	10	30		[illegible]
13th	5	84	16	[illegible]	[illegible]	[illegible]
14th	18	7	[illegible]	14	[illegible]	[illegible]
15th–20th	27	8	18	34	[illegible]	

per cent

e IV *Correlation between fetal life detection at econd ultrasonic examination and later outcome e pregnancy*

of ...y	Detection of fetal life			No signs of fetal life		
	No	Delivery	Abortion	No	Delivery	Abortion
	0	0	0	0	0	0
	0	0	0	4	0	100
	5	100	0	9	56	44
	9	89	11	14	29	71
	11	8	18	8	0	100
	13	83	17	13	0	100
	14	93	7	4	0	100
20th	25	89	11	5	0	100

...ent

weekly prediction for the later course of ...nancy based on fetal life signs can be seen in ... III Until the 12th week the prognosis is ...able in over 90 per cent if fetal life can be de...d at the first examination If the bleeding has ...n later (first examination in the 13th week or ...) the outcome of pregnancy is abortion in ap...imately 20 per cent despite the positive detection ...tal life Yet if no correction is made to the ...ber of gestational weeks (on the basis of the ...tion sac or the biparietal diameter) the false ...tive findings of fetal life signs disappeared only the 12th week In Table IV the weeks of ...nancy have been corrected according to the ...sonic findings at two repeated examinations this correction no false negative findings could ...bserved from the 9th week onwards

...e clinical observations of abortions at the time ...erine evacuation are presented in Table V Of the ...atients for whom the outcome was abortion 134 ...er cent) had the uterine evacuation and curettage ...rmed after information from one or in most ... repeated ultrasonic examinations revealing ... kind of abnormal finding There was no suspi...of an intact normal pregnancy in these cases at

...e V Clinical *observations of abortions at the ... of uterine evacuation*

	Number	Per cent
...aneous abortion at home or in ...tal Only residual tissue in uterus	10?	37
...ible abortion	42	15
...ation made after pathologic ...sonic finding( )	134	48

Table VI *The weeks of delivery*

	<31th	31th–36th	37th–40th	41th–43rd
No	9	11	150	66
%	4	4	64	28

the time of the evacuation In the remaining 52 per cent the abortion occurred spontaneously and curettage was made afterwards The mean interval between the last negative ultrasonic examination and the abortion was 3 2 days in the whole material The pregnancy of 31 patients subsequently ended in spontaneous abortion despite the diagnosis of fetal life signs at the time of the symptoms of threatened abortion The abortion in all these cases occurred in the 12th week or later and the presence of the fetus could be verified in all cases

The weeks of delivery are presented in Table VI The frequency of premature deliveries (before the 37th week) was 8 per cent Seven per cent of the newborns weighed under 2 500 g The rate of perinatal mortality was 3 4 per cent (8 cases) In seven of these cases the main etiologic cause was prematurity Congenital malformations were observed in 9 newborns (4 per cent) Placenta previa at the time of delivery was diagnosed in 3 cases (1 per cent) but no cases of placental ablation were observed The rate of manual separation of the placenta was 6 per cent The sex distribution of the newborns was 119 girls/117 boys

DISCUSSION

The distribution of the final outcomes of pregnancies between abortion and delivery in this series corresponded well to earlier observations in which the prognosis has been successful in about 50 per cent of the cases after threatened abortion (8 9 20) However this series included according to the first ultrasonic examination 92 cases (18 per cent) of incomplete abortion in which the clinical judgement was confirmed by ultrasound before the curettage Thus the truly intact early pregnancies complicated by threatened abortion mostly ended favorably

The duration of bleeding appeared to have a significant effect on the prognosis of the pregnancy Bleeding for 3 days or more predicted abortion almost significantly more often than a shorter bleeding episode This is in accordance with the

earlier observations (8) The week of bleeding onset seemed to have no significant effect although the tendency to abortion increased at a late onset of bleeding This is in slight disagreement with the earlier observations (1 8) but can be explained by the relatively high number of missed abortions at the first ultrasonic examinations (14 per cent) The bleeding in these cases typically begins during the second trimester Also abortions seem to be more common in the patients with positive detection of fetal life from the 13th week onwards compared with the earlier bleeding groups

The most prominent practical finding in the ultrasonic examinations is the prognostic significance of fetal life detection for the later course of pregnancy In this series this diagnosis signified delivery in 87 per cent This percentage corresponds to the earlier observations from the same clinic (9 10) and some other results (5 20) This high predictive value accords primary importance to ultrasonic examinations in the diagnostic evaluation of problems in early pregnancy The interpretation of fetal life findings is simple enough and the results are immediately available for use The occurrence of false negative results ends by week 10–12 which coincides well with the most common onset of bleeding and the admission of patients for diagnostic procedures If there is no doubt about the duration of pregnancy or after reliable correction of this all ultrasonic results are correctly positive and negative after the 9th week

According to the findings made at the first ultrasonic examination the group of blighted ovum is the most common pathologic subgroup (26 per cent) consisting of approximately 50 per cent of all the pregnancies ending in abortion In this series the ultrasonic scanning was repeated in most of the cases where blighted ovum was suspected at the first examination If no fetal echoes or life signs were detected in the gestation sac at the second examination either the diagnosis of blighted ovum was confirmed Thus misinterpretations owing to uncertainty of the duration of pregnancy were avoided and for example a normal finding in the 6th week was not mistaken for a typical blighted ovum in the 10th week This study also emphasizes the importance of a correct determination of gestational weeks Since discrepancies of more than 2 weeks between the anamnestic and the real duration of pregnancy have been observed in 40 per cent of the cases in pregnancy materials (3 14) the correct week must be determined by some ultrasonic methods already in early pregnancy The most exact res[illegible] with the fetal crown rump length ([illegible] biparietal diameter (±6 days) (6) a[illegible] volume (±9 days) (19) The acc[illegible] gestational sac diameter is approx[illegible] (16)

After a detection of fetal life s[illegible] ended in later abortion ([illegible] cent of the cases in which the ex[illegible] invariably confirmed Since the time of [illegible] these cases was relatively late nearly [illegible] cond trimester it is possible tha[illegible] background of these abortions differs [illegible] e g blighted ova Robinson (20) claims [illegible] insufficiency is the main cause of [illegible] abortions as opposed to chromosomal [illegible] earlier abortions A reliable ultrasonic pre[illegible] late abortions at the onset of bleeding [illegible]

In this series the abortion was com[illegible] taneous in 52 per cent after the ultrason[illegible] In the other 48 per cent however the [illegible] evacuated after one or in most cases [illegible] logic ultrasonic findings No doubt [illegible] tion of the intact pregnancies arose [illegible] these 48 per cent (136 patients) the [illegible] pathologic pregnancy with bleeding and [illegible] stress for the patient could be markedly [illegible] This also involves a notable saving of cost

The pregnancies which ended in [illegible] threatened abortion seemed to have a [illegible] complicated late course except for the [illegible] quency of premature deliveries This is [illegible] twice the control rate 4 7 per cen[illegible] during the same period As a co[illegible] higher frequency the perinatal mort[illegible] also increased 3 4 per cent since [illegible] perinatal losses were among the prem[illegible] This is in accordance with the earlier re[illegible] prequency of premature deliveries was [illegible] as high (13–20 per cent) as in some ear[illegible] 8 22) This may be due to the [illegible] pregnancies as risk cases for th[illegible] delivery according to our observa[illegible] study (10) Hence many patients [illegible] very closely during the late pregna[illegible] admitted to hospital for the preve[illegible] delivery

In conclusion one can sta e tha [illegible] diagnostic ultrasonic methods to [illegible] mation on the current sta e of the [illegible] predict with adequate certainty its [illegible]

of threatened abortion Owing to the increased of premature delivery these patients should be rded as risk cases during the later stages of gnancy

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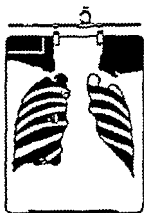
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ALTERATIONS IN THE ELECTROCARDIOGRAM OF THE FETAL LAMB AS A SIGN OF FETAL ASPHYXIA

A comparison between the scalp lead and the precordial lead

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tract Progressive changes in the ST–T period of the electrocardiogram (FECG) were studied in 18 lamb ses acutely exteriorized and subjected to graded hypox he aim of the study was to compare the bipolar precor lead (CR lead) with the unipolar scalp lead and to cor e the alterations in the FECG to blood gas and acid status The scalp lead gave less information regarding l condition and was more difficult to interpret than the ordial lead This might be one factor in the controversy rding the significance of alterations in the FECG during yxia and labor since the scalp lead is used mainly in cal situations Our previous results demonstrating pro- sive changes in the ST–T period of the FECG during oxia in experimental animals and showing the same changes in newborn human infants immediately after 1 were registered with the bipolar precordial lead It is ble that a bipolar scalp lead might give more informa regarding the fetal condition than the unipolar scalp l mainly used in clinical practice

rations in the fetal electrocardiogram (FECG) as ign of intrauterine asphyxia and its diagnostic ie are controversial Although alterations in the tern of the FECG have been detected during ex imental conditions in human previable fetuses (2) l during labor in term fetuses (1 11) these altera is are believed to be preceded by changes of the l heart rate (FHR) (1 3 9 10)

Our own animal experiments have shown pro- ssive changes in the ST T period during graded oxia and these hypoxic changes occurred well in ance of any bradycardia (13) and preceded signs failing cardiovascular function (14) These hypoxic CG changes were found to reflect myocardial gly ysis and early hypoxic stress (6 12) The same G changes were found in newborn babies im diately after birth (4) and were well correlated to cardiotocographic pattern during labor and the ical condition of the child after delivery (5) These ECG recordings were registered with a bipolar pre cordial lead In clinical practice however the FECG is registered mainly by the use of a vaginal electrode giving an unipolar scalp lead The different ways of exploring myocardial electric activity might explain the controversy regarding the value of the FECG as an indicator of fetal well being during labor

The aims of the present study were to compare the values of the unipolar fetal scalp lead and the bipolar precordial lead (CR lead) during graded hypoxia in lamb fetuses and to correlate the FECG-changes to blood gases acid base status and cardiovascular functions

METHODS

The experiments were conducted on 14 ewes of mixed breed with 18 fetuses Their gestational age was 120±4 days (mean value±SEM) and ranged from 94 to 140 days (term 147 days) The gestational age was either dated or estimated from fetal weight and crown rump length using standard curves (7) The fetal weight was 1 948±204 g and ranged from 619 to 3 370 g The fetuses were acutely exteriorized The anesthesia was induced with pentothal (50 mg/ml 0 1 ml/kg) and was maintained with chloralose (25 mg/ml 1 4 ml/kg) The anesthesia and preparation method have been described earlier by Rosen *et al* (14)

The fetal ECG was recorded as a bipolar precordial lead (CR lead) with lead electrodes of a diameter of 0 8 cm plac ed subcutaneously The exploring electrode was placed on the left part of the chest between the apex and the left part of the sternum the indifferent electrode on the right foreleg and the common ground on the right hindleg In 15 fetuses the FECG was also recorded as an unipolar scalp lead with the electrode placed subcutaneously in the parietal region and the common ground connected to the metal table on which the fetus was placed and in 3 fetuses it was recorded as a bipolar scalp lead with electrodes in the scalp and precordium and the common ground connected to the metal table The FECG impulses were recorded on a Grass poly graph 7 recorder

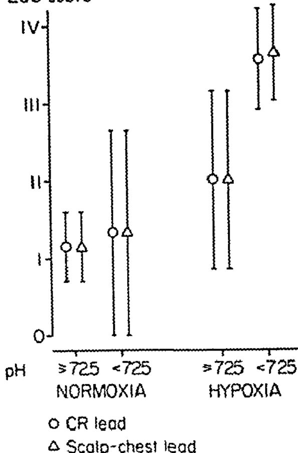


Fig. 5. The FECG score in relation to hypoxia and acidosis. Comparison between bipolar scalp-chest lead and CR lead (mean values±SEM).

always exceed that of the P wave. A scattergram of the T/QRS ratios is demonstrated in Fig. 3. The correlation coefficient between all the 74 observations is 0.51 ($p < 0.001$).

Bipolar scalp-chest lead. The bipolar scalp-chest lead was used in 3 fetuses. Thirty-one sets of observations at varying pO_2 and pH values were made. The material was divided in different groups in the same manner and mean values of pO_2 and pH in the different groups are shown in Table II. The bipolar scalp-chest lead gave quite as good technical quality as the CR lead. It gave a good correlation to the precordial lead both as measured as T/QRS ratio with a correlation coefficient of 0.92 (Fig. 4) and as the scoring system with the highest scores in the group with both hypoxia and acidosis (3.55±0.65 resp. 3.64±0.62, mean values±SEM) (Fig. 5).

DISCUSSION

In an endeavour to detect fetal hypoxia [illegible] been focused on alterations in the fetal [illegible]diogram but its diagnostic value is [illegible] present results are in accordance [illegible] findings that the bipolar precordial FECG [illegible]tains information regarding fetal [illegible] acidosis both when the full configuration [illegible] period and when the T/QRS ratio [illegible] The unipolar scalp lead however gave [illegible] which were more difficult to interpret. The [illegible] was more often unstable, the QRS-com[illegible] lower and the technical quality of the sca[illegible] not as good as the precordial lead. Th[illegible] system applied to the scalp lead did not [illegible] well with fetal hypoxia and acidosis as the [illegible] The T/QRS ratio of the scalp lead gave a [illegible] better correlation with the fetal situation, the [illegible] ratios occurring when the fetuses were both [illegible] and acidotic. Since the QRS-complexes were [illegible]ly small in the scalp lead, small elevations of [illegible] wave gave higher T/QRS ratios but did not [illegible] higher since the T wave amplitude did not [illegible]ceed that of the P wave. Thus the [illegible] was inferior to the bipolar precordial lead [illegible] fetal hypoxia and acidosis, yet it seems to be [illegible] to pick up ST-T changes using the sca[illegible] exploring electrode. A bipolar scalp-chest lead [illegible] quite comparable with the precordial lead.

Alterations in the FECG have been rep[illegible]ing labor and with the aid of the sca[illegible] computer analysis when the FECG [illegible] considerably improved (8, 11, 15) [illegible] ferences of opinion about the interpretation [illegible]tions in the FECG during labor and [illegible] general consensus of opinion is that [illegible] the configuration of the FECG are [illegible]ed changes in the fetal heart rate (1, 3, [illegible]

Table II. *pH and pO_2-values in d[illegible] (mean values±SEM) using the [illegible] lead*

	pO_2 (kPa)	pH	[illegible]
Normoxia without acidosis	3.31±0.1	[illegible]	[illegible]
Normoxia with acidosis	3.12 0.19	[illegible]	
Hypoxia without acidosis	[illegible]	[illegible]	
Hypoxia with acidosis	1.6 0.11	[illegible]	

We have earlier shown in animal experiments that anges in the ST T period of the FECG are an early n of fetal hypoxia and that the same kind of ECG anges previously observed in animal fetuses exist ely post partum in newborn human babies e precordial bipolar CR lead was used both in animal experiments and in the newborn babies e present findings that the FECG registered with unipolar scalp lead gives less information and is re difficult to interpret might explain the con versy regarding the value of alterations in the CG during labor and asphyxia and it might be rthwhile trying some kind of bipolar scalp lead ring labor in clinical conditions

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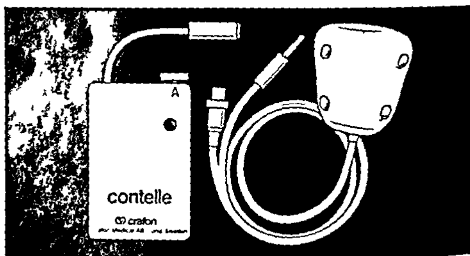
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RADIOIMMUNOASSAY OF SERUM BILE ACIDS IN NORMAL PREGNANCY AND IN RECURRENT CHOLESTASIS OF PREGNANCY

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tract Radioimmunoassay has been used to quantitate conjugates of cholic and chenodeoxycholic acid in ous blood from women in different stages of normal and in patients with recurrent intrahepatic estasis of pregnancy (RCP) The levels of cholic and odeoxycholic acid were shown to be within normal ts throughout uncomplicated pregnancy and elevated in Because of RIAs simplicity and reliability it is sug that this method can be used to detect and follow the se of RCP and to assess the possible influence of treat t e g diet

cholestasis of pregnancy (RCP) is charac ed patho-physiologically by intrahepatic chole is of varying degree and elevated levels of bile is in blood is one of the main features of the ase (8 14) Recently methods based on quantita of individual bile acids by computerized GC/MS made it possible to study changes of the urinary etion of bile acids in great detail (1) The quanti ely important role of the primary bile acids chol chenodeoxycholic acids in RCP has been con ned (16 17) The complexity of these methods ever precludes their use in clinical routine work Methods for determining conjugated bile acids in by radioimmunoassay (RIA) have been in use more than 5 years and have proved to be sensitive ly specific simple and reliable (4 13) In order to uate the clinical use of bile acid determinations in P a study has been made in which the concentra s of cholic and chenodeoxycholic acid conjugates rum measured by RIA have been compared with excretion of these bile acids in urine determined GC/MS

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reviations and trivial names cholic 3α 7α 12α trihy y 5β-cholanoic and chenodeoxycholic 3α 7α-dihy y 5β-cholanoic acid Recurrent intrahepatic cholestasis regnancy is abbreviated RCP radioimmunoassay RIA as chromatography mass spectrometry GC/MS

MATERIAL AND METHODS

Normal subjects Blood levels of conjugated cholic and chenodeoxycholic acid were determined 4 times during the last two trimesters of eight normal pregnancies Venous specimens were taken in the morning after overnight fast ing All of the women subsequently had normal deliveries

A second group of normals consisted of twenty three pregnant women who were admitted to the delivery ward at term Some of these were already in labor others were ad mitted for induction None of the subjects had any disease with possible liver engagement (e g toxaemia diabetes) and all had been fasting for 8 hours before sampling The deliveries were normal

RCP patients Five patients with general itching and the clinical diagnosis of RCP were studied with analyses of con jugated cholic and chenodeoxycholic acid in blood (after overnight fasting) total excretion of bile acids in urine and conventional liver function tests once during the last preg nancy month (patients A B C E F) Apart from RCP the pregnancies and subsequent deliveries were normal Two more patients (D and G) were followed during the last two trimesters at 4 week intervals with the same type of sampl ing Details of urinary bile acid excretion in these two pa tients have been published (17)

Finally three women (patients H I K) with a history of general itching in previous pregnancies were followed dur ing the two last trimesters with venous blood taken at mon thly intervals They all developed general itching after the 33rd pregnancy week In these cases the samples were taken in the morning after a light breakfast

Radioimmunoassay Blood was drawn into heparinized glass tubes from an antecubital vein and centrifuged The plasma was stored at -20 C until analyzed Unsulfated glycine and taurine conjugated cholic and chenodeoxychol ic acid were determined according to Simmonds *et al* (13) The method with a few minor alterations has been described (12) Crossreactions with other bile acids were negligible The range in healthy fasting subjects is $0\ 1 - 1\ 0$ µmol/l for cholic acid conjugates and $0\ 2 - 2\ 0$ µmol/l for chenodeox ycholic acid conjugates

GC/MS analysis Urine was collected during a 24-hour peri od and kept frozen during the collection period by storage on dry ice After thawing and measuring aliquots were stored at -20 C until analyzed Separation of the bile acids according to conjugate groups and computerized GC/MS quantitation of individual bile acids were achieved by the method of Alme *et al* (1) Normal upper limits for cholic and chenodeoxycholic acid were $1\ 0$ µmol/24 h and

Table I *Fasting serum levels (µmol/l) of conjugated cholic (S C) and chenodeoxycholic (S-CDC) acid [illegible] mal pregnancy*

Pregnancy week	16–22		23–27		28–32		33–[illegible]	
	S-C	S CDC	S-C	S-CDC	S-C	S-CDC	S-C	S-[illegible]
Subject								
1	0 48	2 15	0 16	0 41	0 15	0 70	0 4	[illegible]
2	0 10	0 20	0 14	0 62	0 40	0 46	0 23	[illegible]
3	0 22	1 60	0 83	3 70	0 70	2 15	0 1	[illegible]
4	0 70	0 31	0 35	1 15	0 52	1 60	0 31	[illegible]
5	0 60	1 25	0 34	0 65	0 28	0 7[illegible]	0 90	[illegible]
6	0 16	0 22	0 23	0 75	0 70	0 5[illegible]	0 50	[illegible]
7	0 27	1 15	0 20	0 88	0 21	0 80	0 23	[illegible]
8	0 35	1 40	0 20	0 37	0 27	0 85	0 36	[illegible]
Mean	0 36	1 04	0 31	1 07	0 34	0 93	0 4	[illegible]

See text

1 0 µmol/24 h respectively (1 16) No differences in these values were observed between healthy non pregnant and pregnant women

Routine liver tests Serumaminotransferases (S-ASAT and S-ALAT) and serum alkaline phosphatases (S-ALP) were determined according to (15) and serum bilirubin (S-Bil) was measured with a Technicon multichannel analyzer

RESULTS

Serum bile acids in normal pregnancy Table I shows the result of serial determinations of cholic and chenodeoxycholic acid conjugates in the second half of eight normal pregnancies All values except two are within the normal range Subject 3 showed slightly increased levels of chenodeoxycholic acid on two occasions probably because she had been breaking the fast before sampling However even on these occasions the levels of cholic acid were normal Significant increases of the values towards the end of pregnancy were not observed

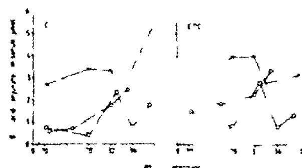


Fig 1 Serum levels of conjugated cholic (C) and chenodeoxycholic (CDC) acid in three patients H (x – x) I (O – O) and K (– –)

The range of conjugated cholic acid in [illegible] en examined during delivery was 0 15–0 [illegible] (mean 0 43 µmol/l SD 0 22 µmol/l) The corresponding chenodeoxycholic acid range was [illegible] µmol/l (mean 0 86 µmol/l SD 0 37 µmol/l)

Serum and urinary bile acids in patients wi[illegible] The relationship between serum levels and excretion of cholic and chenodeoxycholic acid is seen in Table II

Fig 1 shows the serum levels of conjugated cholic and chenodeoxycholic acid in the last [illegible] patients H I and K The values are seen to [illegible] in each of the patients Thus in these cases of cholestasis the cholic/chenodeoxycholic [illegible] in serum was relatively constant

The levels of cholic and chenodeoxycholic acid in blood and the excretion of these bile acids [illegible] from patients D and G are compared in Fig [illegible] cholestasis advanced and bile acid levels [illegible] started to rise the ratio of cholic to chenodeoxycholic acid increased The same phenomenon was [illegible] in urine

Routine liver tests The levels of serum aminotransferases alkaline phosphatases and bilirubin [illegible] determined in the patients A–G As shown in [illegible] II there was no correlation between these [illegible] and the levels of serum cholic and chenodeoxycholic acid

DISCUSSION

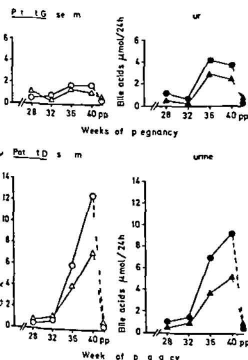
Our study confirms earlier results [illegible] serum levels of conjugated cholic and chenodeoxycholic acid are normal in uncomplicated [illegible] (7 14) The methods in previous studies [illegible] on quantitation by gas chromatography [illegible]

ıle II *Primary bile acids in serum (S C and S CDC) and urine (U C and U CDC) and conventional liver ction tests in ten patients with RCP Normal values are shown within brackets Serum bile acid levels in pa ts A—G are fasting levels those in H—K are not*

ʼent	Age	Pregnancy week	S-C (<1 0 µmol/l)	S-CDC (<2 0 mol/l)	U-C (<1 0 m l/24h)	U-CDC (<1 0 mol/24h)	S-ASAT (<0 7 µkat/l)	S-ALAT (<0 7 µkat/l)	S-ALP (<4 kat/l)	S-Bil (<21 µmol/l)
	22	35	54 0	12 0	170 1	58 5	1 45	3 06	13 2	38
	30	40	35 0	10 0	100 2	57 4	1 38	3 00	11 1	19
	23	38	16 0	12 0	32 5	30 5	2 16	3 70	14 6	15
	28	39	12 5	7 2	9 3	5.2	2 87	7 64	9 1	5
	27	40	12 0	8 0	4 6	6 8	0 51	0 71	11 6	9
	24	36	2 3	2 2	2 3	3 5	0 67	1 28	2 7	10
	31	37	1 7	1 1	4 1	3 0	0 63	1 14	6 3	7
	29	40	5 5	3 1						
	29	35	2 5	3 4						
-	27	39	1 8	1 4						

ıs value is normally elevated during pregnancy

ıer with the necessary steps of purification and lrolysis makes these methods time-consuming and refore impracticable in clinical use It should be ınted out that with our RIA method the total ounts of glycine and taurine conjugates and ɔut 50 per cent of the unconjugated bile acids are determined but not the sulfated bile acids However since practically 100 per cent of cholic and about 90 per cent of chenodeoxycholic acid in serum are conjugated with glycine or taurine (10) omission of a time-consuming solvolysis seems justified Also in preliminary experiments RIA determinations of cholic and chenodeoxycholic acid in serum were in good agreement with analyses by gas liquid chromatography after solvolysis



ʼ 2 Conjugated cholic (○ – ○) and chenodeoxycholic – △) acid in serum (after fasting) determined by RIA and ıl cholic (□ – □) and chenodeoxycholic (▲ – ▲) acid in ıe determined by GC/MS in two patients D and G with P

After a test meal cholic and chenodeoxycholic acid differ in absorption and hepatic turnover (2 12) Cholic acid describes a small peak 60–90 minutes after the meal and a rapid decline In contrast serum levels of chenodeoxycholic acid increase more rapid ly with a high peak after 30–60 minutes and decline slowly to fasting levels Subject 3 in Table I illustrates this difference between the two acids Probably be cause of variation in time between meals and sam pling chenodeoxycholic levels exceeded normal values on two occasions Cholic acid apparently cleared more rapidly after meals was within normal limits on both occasions Therefore RIA determina tions of cholic acid conjugates in serum might be preferred as the routine method for serial analyses in e g recurrent cholestasis of pregnancy

Bile acid determinations in RCP Clinically RCP pa tients can be divided into three groups I pregnant women with general itching only II patients with general itching and elevated serum aminotransferase levels III patients with general itching and elevation of serum aminotransferases as well as conjugated bilirubin (jaundice) Apart from the clinical assess- ment the serum aminotransferases and especially alanine aminotransferase (S-ALAT) have been the best routine methods for following intermediate and

serious cases of RCP (5) Recent studies however have shown that there is a poor relationship between the levels of serum aminotransferases and changes in bile acid metabolism as judged by the excretion pattern of bile acids in urine (16) It seems reasonable to assume that the determinations of bile acid levels in either bile (9) serum (8) amniotic fluid (3) or urine (16) reflect the degree and course of RCP better than any method in use today Table II and Fig 2 show the positive relationship between levels of conjugated cholic and chenodeoxycholic acid in blood and total urinary excretion of these bile acids No such relations could be seen between any of the bile acids and the conventional liver function tests except in the case of patient A who had pathologically elevated serum levels of bilirubin

Some studies indicate that RCP may represent a danger to the fetus (6 11) A method for quantitative serial analyses of the degree of liver involvement in RCP would be of value in assessing the effect of treatment and in deciding whether or not labor should be induced The simplicity and reliability of RIA determinations of bile acids in serum seem to make this method the best one at present for monitoring the course of RCP It may also make it possible to study the effects of other complications of pregnancy e g toxaemia on the levels of bile acids in blood

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OXYTOCINASE ACTIVITY IN THE COURSE OF CONTINUOUS LUMBAR EPIDURAL ANALGESIA

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ract The oxytocinase activity in the blood serum ilical blood and homogenates from the placenta and ilical cord was determined in 34 women in labor cted to continuous lumbar epidural analgesia with 5 per cent bupivacaine and 1 800000 epinephrine The s obtained were subjected to statistical analysis and pared with a group of 30 patients in spontaneous labor out any drugs Significantly higher oxytocinase activity found in the women subjected to epidural analgesia increased oxytocinase activity was found to correlate the duration of the first stage of labor It is assumed the increase in the oxytocinase activity in the course of inuous epidural analgesia is associated with diminished ne contractions and is related to the effect of the cular anesthetic agent

tocinase (EC 3 4 11 3) the specific enzyme caus- a loss of the biological properties of oxytocine is rded as one of α amine acyl hydrolases of pep- s Immunohistochemical studies by Watkins & ll (17) showed that oxytocinase which controls oxytocine level of the blood is localized in the ytial cells of the placenta and secreted into the in illous spaces According to Branda & Ferrier (3) is accomplished through enzymatic inactivation he neurohormone and its degradation in the tis The action of oxytocinase in processes related to maintainance of pregnancy initiation of labor its course is beyond any doubt (8) Ances (1) has lished observations concerning the behavior of tocinase activity in the course of spontaneous r The purpose of the present paper is to establish behavior of oxytocinase in the course of labor ing epidural analgesia While the effect of the epi al analgesia on uterine contractility has been rved by several authors e g Cooper *et al* (5) wford (6) Schifrin (12) the pertinent literature fails to describe the mechanism involved

MATERIAL AND METHODS

At the Institute of Gynecology and Obstetrics Wroclaw Medical Academy 34 primiparae were subjected to continuous lumbar epidural analgesia Analgesia was induced with 0 125 per cent bupivacaine and 1 800000 epinephrine at the onset of the active phase of labor (2) The lumbar epidural analgesia was carried out in all cases by Prof dr habil A Aronski head of the Interclinic Department of Anesthesiology and Resuscitation Wroclaw Medical Academy The control group was made up of 30 primiparae with spontaneous labor and no drugs There were differences as to age clinical laboratory and environmental data between the experimental and control groups

The oxytocinase activity in the blood was determined on four occasions on each patient before the onset of clinically detectable labor (A) at the active phase of labor (B) at full dilatation of the cervix (C) and two hours post partum (D) In both groups the oxytocinase activity was determined in the umbilical blood and in placental and umbilical homogenates

The present method of determining the enzymatic activity is a modification of that reported by Tuppy & Nesvadba (15) and has been described earlier (19) The method is bas

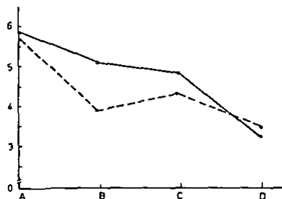


Fig 1 Serum oxytocinase activity in different phases of labor A Prior to labor B Active phase of labor C Full dilatation of the cervix D Two hours post partum — Epidural group -- Control group Oxytocin activity in IU/l

Table I *Oxytocinase activity in the blood serum and umbilical blood of women dur[illegible] spontaneous labor*

Time of determination	Epidural group Mean	SD	Control Group Mean	SD	Test of significance $p<0.001$
Prior to labor	5 81	1 51	5 69	1 94	–
Active phase of labor	5 12	1 41	3 94	0 81	+
Full dilatation of the cervix	4 89	1 50	4 30	1 69	+
Two hours post partum	3 17	1 44	3 50	1 59	+
Umbilical blood	1 53	0 70	1 07	0 33	+

Expressed in IU/l

ed on the use of L-cystine-di β naphthylamide from Koch Light Lab England as a substrate and colorimetric determination of the β naphthylamine released with p-dimethyl aminobenzaldehyde in presence of acetic acid Oxytocinase activity is expressed in IU/l The duration of labor was also evaluated as were the contractility of the uterus and the fetal and placental weights the results were subjected to statistical analysis

RESULTS

The results are given in Table I and Fig 1

Comparison of the oxytocinase activities before labor (A) in the epidural group (5 81±1 51 IU/l) and control group (5 69±1 94 IU/l) shows similar values the differences being insignificant In the active phase of labor (B) the mean oxytocinase activity in the epidural group is 5 12±1 41 IU/l which is significantly higher than that in the control group with a mean value of 3 94±0 81 IU/l In both groups the observed reduction in oxytocinase activity is related to the *increase in the level of the* circulating oxytocine which is lower in the epidural and higher in the control group and results in accelerated contractility of the uterus

At full dilatation of the cervix (C) the mean oxytocinase activity in the epidural group amounts to 4 89±1 50 IU/l and is statistically higher than that in the control group with a mean 4 30±1 69 IU/l

The determinations performed two hours post partum (D) were 3 17±1 44 IU/l in the [illegible] ±1 59 IU/l in the control group both [illegible] similar decreasing tendency (Fig 1)

The oxytocinase values of the umbilical [illegible] *hibited significant in both groups* In the [illegible] group the mean oxytocinase activity was 1 5[illegible] IU/l against 1 07±0 33 IU/l in the control [illegible] cant increase of 50 per cent oxytoc[illegible] epidural group correlated well with the [illegible] oxytocinase in the blood serum of [illegible] analgesia

The oxytocinase activity of placental [illegible] as expressed in terms of IU/g of protein [illegible] statistically significant differences, it was [illegible] IU/g in the epidural group and 0 9[illegible] 0 3[illegible] controls and correlated well with the [illegible] and fetal weight (Table II and III)

Analysis of the duration of [illegible] labor revealed a significant prolo[illegible] stage in the epidural group [illegible] 713 min against 583 min in the co[illegible] ference was corroborated by s[illegible] the expression of a reduction in the co[illegible] the uterus related to the analges[illegible]

In both groups the differences be[illegible] tion of the second and third stages of labor [illegible] significant (Table IV)

Table II *Oxytocinase activity in homogenates from the placenta and umbilical cord*

Site of determination	Epidural group Mean	SD	Control group Mean	SD	Test of significance $p<0.001$
Placenta	0 89	0 4[illegible]	0 9[illegible]	0 31	–
Umbilical cord	0 76	0 23	0 70	0 38	–

expressed in IU g of protein

le III *Fetal and placental weights (g)*

	Epidural group		Control group	
	Mean	SD	Mean	SD
	3495 00	452 16	3386 00	367 16
nta	536 47	97 75	551 00	81 42
ficance 0 001	+		+	

DISCUSSION

control group the results of studies of oxyto- activity in the course of labor are consistent hose observed in spontaneous labor by Ances ho used a similar technique The corresponding ninations from the epidural group are different ularly in the active phase of labor and at full tion since the average oxytocinase activity is r than that in the controls The increase in oxy ise activity in the epidural group was also ac anied by temporary decrease in contractility of erus This fact is evidenced by a mean prolonga of the first stage of labor of 130 min in the epi group which has also been observed by other rs (10 11, 14 18)

concomitant increase in the oxytocinase activity blood serum of patients in the epidural group is uggested by the correspondingly higher oxyto- activity (higher by 50 per cent) in the umbilical from the same group The lack of differences oxytocinase activity of placental homogenates lood serum in both groups implies that changes oxytocinase activity during labor are closely d to the analgesia and agents used

ack *et al* (16) and Steenberg (13) when studying ontractility of the uterus in patients during the phase of labor failed to find a correlation with acaine concentration The studies of Epstein *et*) revealed no correlation between the concentra of 1–2 per cent prilocaine and its blood level on ontractility of uterus He agrees however with Bromage (4) who states that there is little evidence to suggest that epinephrine in a concentration of 1 200000 has a deleterious effect on labor if a low dose lumbar epidural technique is used Nicholas *et al* (9) demonstrated that 0 25 per cent bupivacaine with 1 400000 epinephrine had no effect on the dura tion of uterine contractility

Epinephrine is however known to cause a rapid and short lasting strong contraction of blood vessels in all organs The changes in the oxytocinase activity of the blood serum and umbilical blood from the epi dural group during labor on the one hand and the lack of such changes in the post partum period and in the homogenates on the other constitute further con firmation of the observation that epinephrine is al most immediately degreaded by phenolase and ami nooxydase

Although the influence of various factors related to labor and the contractility of the uterus (e g pro- gesterone estrogen nervous anatomic or psychic ef fects) interferes with the evaluation of analgesic agents the statistically established increase in ox ytocinase activity seems to be one of the links in the chain of events leading to disturbed or diminished contractility of the uterus

The present studies are a step towards a better understanding of complex and interdependent mechanisms which require further investigation

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e IV *Duration (min) of stages of labor in epidural and control groups*

p	First stage		Second stage		Third stage	
	Mean	SD	Mean	SD	Mean	SD
ural	713 16	534 08	56 32	40 57	6 50	5 48
rol	583 08	177 17	55 16	41 42	6 13	3 07
ficance 0 001	+		–		–	

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ECTOPIC PREGNANCY AND IUDs INCIDENCE RISK RATE AND PREDISPOSING FACTORS

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stract During a period of 4 years 1974–77 in Uppsala nty Sweden 03 women underwent surgery for ectopic gnancy with histological proof of the diagnosis For the ale population of fertile age this corresponds to 0 11 ec ics per 100 women 15–44 years of age or 1 03 per 100 ified pregnancies or 1 53 per 100 births Fifty five of the men with ectopic pregnancy were using an intrauterine ice (IUD) (48 a copper bearing IUD and 7 some other of device) and 6 women used a low dose progestogen traceptive For users of copper bearing IUDs the risk of ectopic pregnancy was estimated to be 0 15 per 100 men years When comparing this latter risk rate with the rall incidence rate of 0 11 it must be observed that the ulations forming the denominator in these two rates dif with respect to some crucial characteristics Nulliparity predisposing factors were found statistically significant nore of en in non IUD-users with an ectopic pregnancy n in IUD-users Such predisposing factors may be less valent in IUD-users as in other populations This may lain why ectopic pregnancy has been found to occur less quently than theoretically expected among IUD-users ectopic preventing capacity of the IUD may refore be considerably lower than has been previously med

incidence of ectopic pregnancy is known to vary m population to population and also for users of ferent contraceptive methods including no thod (7) Apart from obvious differences in the de of action for different contraceptive methods i might in part be explained by differences in the valence of conditions predisposing to ectopic gnancy (1) In this paper we report findings on the valence of ectopic predisposing factors in women h ectopic pregnancy with and without an IUD l present the incidence in a defined geographical a of Sweden and the estimated risk rate for ec ic pregnancy for users of copper bearing IUDs

MATERIAL AND METHODS

m registers kept in all the hospitals in Uppsala county ден every woman who had undergone surgery for ec ic pregnancy during the period 1974–77 was identified Their records were examined with respect to the history of previous pregnancies infertility problems tubal surgery other abdominal surgery pelvic inflammatory disease (PID) and the use of contraceptive method at the time of the ectopic pregnancy The occurrence of tubal adhesions found during the operation was noted The validity of the diagnosis of ectopic pregnancy was evaluated Only those women who had histological proof of the diagnosis were included All women were sent a questionnaire about the use of contraceptives at the time of their ectopic pregnancy and their history of PID prior to the operation

Based on detailed sale statistics for copper-bearing IUDs in the county which we obtained from the wholesal firms we estimated the number of one year-users of this contraceptive method The figures on sale statistics were reduced by 10 per cent to cover devices returned by retailers and IUDs discarded because of contamination In addition the estimation takes into account the discontinuation rates per year We have used the discontinuation rates for IUD-users given by Mishell (6) which are of the same magnitude as those found for users of copper bearing devices in a recent clinical trial in our department (5)

The size of the female population 15 to 44 years and the number of births and legal abortions were found in official demographic statistics (9 10 11) The number of spontaneous abortions was collected from registers in the hospitals of the county

RESULTS

During the years *1974* to *1977* a total of *203* women in Uppsala county underwent surgery for an ectopic pregnancy with histological proof of the diagnosis All the patient records were found and examined The questionnaire was answered by 97 per cent of the women

Six ectopic pregnancies occurred among users of a low dose progestogen contraceptive Fifty five women reported use of an IUD at the time of their ectopic pregnancy Of these women 48 used a copper bearing IUD and 7 some other type of device Among women using other contraceptive methods than oral contraceptives (OC) IUDs or no contraceptive at all (non-OC-or IUD-users) we registered 142 ectopic pregnancies For the 6 women (3 per cent of

Table I *Incidence of ectopic pregnancy Uppsala county 1974–77*

Measure of incidence	Rate
Ectopics per 100 intrauterine pregnancies	1 08
Ectopics per 100 births	1 53
Ectopics per 100 women aged 15–44 years	0 11

the total number) who did not answer the questionnaire we obtained information on the use of OC or IUD from their medical records The correlation between the answers to the questionnaire and the medical record information was high We found contradictory information with regard to previous PID in only 3 of the women not using OCs or IUDs According to their records two of these women had been hospitalized for PID For the third woman we relied on her information from the questionnaire in which she denied previous PID

The mean age for IUD users with an ectopic pregnancy was 27 8 years ± 5 2 and for non OC or IUD users 27 7 years ± 4 8

From 1974 to 1977 the number of notified intrauterine pregnancies in the county was 18 773 (13 277 deliveries 1 218 spontaneous abortions and 4 278 legal abortions) In Table I the incidence of ectopic pregnancy in the county during the observed period is presented For users of copper bearing IUDs the risk of ectopic pregnancy was estimated to be 0 15 per 100 women years

In Table II the recorded variables relating to the previous pregnancy and any history of events which may have interfered with fertility for both IUD users and for non OC or IUD users having an ectopic pregnancy are listed (The small number of women using a low dose progestogen is excluded in this context) The table shows that the number of [illegible] with one or more predisposing factors was 18 ([illegible] per cent) of the IUD users and 94 (55 per cent) of the non OC or IUD users ($p < 0\ 001$)

During the laparotomy for ectopic [illegible] fewer adhesions were recorded for IUD-users [illegible] pared with non OC-or IUD users in 13 ([illegible] per cent) of the IUD users and in 66 (46 per cent) of the non OC or IUD users tubal adhesions were recorded ($p < 0\ 005$)

DISCUSSION

Recently Aznar *et al* (1) have assessed the [illegible] problems concerned in the evaluation of a[illegible] association between ectopic pregnancy and [illegible] IUDs They point out that the ratio of ectopic [illegible] trauterine pregnancies which is usually [illegible] *describe the incidence of the former* [illegible] knowledge concerning the actual risk for [illegible] these contraceptives For IUD-users this ratio [illegible] affected by a contraceptive-dependent reduc[illegible] the intrauterine pregnancy rate Therefore [illegible] *al* suggest that the incidence of ectopic preg[illegible] should be expressed as life table rates per 100 [illegible] years They also stress that predispos[illegible] vary between users of different contra[illegible] methods This latter suggestion is probably be[illegible] firmed or rejected by careful case control studies [illegible] prevalence of predisposing factors in women [illegible] topic pregnancies using different contra[illegible] methods would indicate whether this suggestion [illegible] relevance

In our county the incidence of ectopic preg[illegible] was found to be 0 11 per 100 women 15–44 years [illegible] age or 1 08 per 100 notified intrauterine preg[illegible] or 1 53 per 100 births This incidence is [illegible]

Table II *Recorded variables in women with ectopic pregnancy by contraceptive method Uppsala co[illegible] 1974–77*

Variable	IUD users (n = 55)	Non OC-or IUD users (n = 14)	χ^2_{1DF}	
Previous birth	43	85	5 071	p<[illegible]
Previous spontaneous abortions	6	15	0 035	NS
Previous legal abortions	6	18	0 009	NS
Previous PID	13	53	2 749	p<[illegible]
History of infertility	1	41	15 7?4	p<[illegible]
Previous tubal surgery	0	24	9 065	p<[illegible]
Other abdominal surgery	8	34	1 565	NS
One or more predisposing factor	18	94	16 766	p<[illegible]

χ^2 values computed with continuity correction

ıer than that found ın Turku Finland for ı–75 (1 23 ectopics per 100 births or 0 83 per 100 gnancies) (2) but somewhat lower than the ın nce reported by Hallatt California USA for ı–75 (1 85 ectopics per 100 births) (3)

he estimated risk of ectopic pregnancy for users copper bearing IUDs was 0 15 per 100 women s Our estimated risk is therefore of the same gnitude as reported by Lehfeldt *et al* for a popula in the USA (0 1 per 100 women years) (4) and sey *et al* for a British population (0 12 per 100 nen years) (8)

We find that the overall incidence of ectopic preg ncy for women in the fertile age span and the es ated risk for users of copper bearing IUDs within same population are of the same magnitude en comparing these rates it must be observed ever that the denominator in the overall in nce rate comprises women of whom a large pro tion are not at risk of conceiving (sexually inac sterile and pregnant women) or women at a very risk (women using combined OCs) whereas the ominator in the risk rate for IUD users consists of sexually active women continuously at risk of ceiving These differences in the population esenting the denominator in our rates make n unsuitable for comparison

Considering the women with ectopic pregnancy we nd less nulliparous women and fewer women with istory of ectopic promoting factors in IUD s than in non OC or IUD users These findings in accordance with those reported by Hallatt (3) Erkkola & Liukko (2) They also found pre osing factors occurring more often in non IUD s than in IUD users Some of these factors such nfertility problems history of salpingitis Fallop- tube surgery *for infertility and adhesions* are cer ly linked and more than one of these factors was orted for some of the women Nevertheless in our ly the proportion of IUD-users *with an ectopic* gnancy without one or more predisposing factors statistically significantly larger than the propor of non-OC-or IUD-users with an ectopic preg cy presenting with no such factor

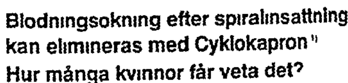
has been claimed that in the presence of an IUD al implantation of a fertilized ovum is reduced by ut 95 per cent (4) This assumption is based on the erence between expected and observed number of opics in IUD-using women Such a calculation s not take into account any factors such as a ble linkage between the choice of an IUD for contraception and a low prevalence of ectopic pro- moting conditions A low prevalence of conditions predisposing for ectopics in IUD users which our results suggest could explain why they occur less fre quently than expected among users of this contracep- tive method The ectopic preventing capacity of an IUD may therefore be considerably lower than previ ously claimed We find it reasonable therefore to avoid recommending IUDs as a method of contracep- tion in women with known ectopic predisposing con ditions

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Blodningsokning efter spiralinsattning kan elimineras med Cyklokapron[1] Hur många kvinnor får veta det?

1) *Rybo* G The IUD and endometrial bleeding J Reprod Med 20 (1978) p 175

Cyklokapron (tranexamsyra) tabl 0 5 g och mixtur 0 1 g/ml

Cykl kap on ä en f b i olyshämma e och inn håller som akt s ţqstans t anexamsy a som ha en k aftigt hämmande ef kt på plasminogenakt e ingen dvs om vandl gen a pl sm noge till plasm n
T a e amsy a ha ca 10 gå ge k aftiga e ant f bnnolyt sk akt tet än am nokap onsy a (Eps kap on) Cyklokap on f nns som tablette mi tu och njekt o slösn ng
Indikatione Blödn ng elle blöd ngs isk v d ökad fibrinolys ell f bn og nolys He ed tärt ang oneu ot skt ödem
Kontraindikationer Försikt ghet bö iakttagas vid ju insuff c ens på grund a sk lö ackumulat on och v d k aftig hematu f ån d ö e urin ägarna då i e stake fall avflödesh nder dessa akttag ts Pat ente med uttalad t ombosrisk bö ej ges Cyklokap on såvida icke samtid g behandl ng med a t koagulant a kan äga um P epa a ets ofarl gh t d g av d tet å ännu te kl skt bek äftad V d rubbat fä gseende bö p epa atet ej insättas Skulle ubbat fä gsee de ppt äda u de på gående behandl g bö p epa at t utsättas
Bi erkninge Gastro ntestinala besvä (llamående kräk gs d arré) fö ekomme men forsvinner då dos n m nskas Enstaka fall a yrsel elle blodtrycksså kning ha rapporte ts
Att beakta på grund a djure perime t lla fynd På hund ha ret nalo å dn ga erhåll ts efte långvarig tillförsel a sto a dose t an amsy a och på katte e intravenös i jekt on a 250 mg per kilo kroppsvikt d g under 14 daga Sådana fö ä d nga ha ej erhå l ts vid nder sökn ng på råtta vid t llförsel a max mal tolererad dos Inga ret nalö ä dri ga ha rapportera t efter konstate ats v d ögonkontroll på pat ente som behandlats med Cyklokap on unde fle a eckor t ll må ader På pat ente som skall behandlas kontinuerligt under flera eckor lö etages lämpl gen oftalmolog sk kontroll (b. a synskärpa fä gsee de ögonbottnar synfält) om mö innan behandl gen påbörjas och regelb ndet under behandl ngen
På en ätts am ha gall ägshyperplasi och en par fall av lev adenoca ci om rapporte a s efte 22 månaders pe o ai tillförsel a ma mall tole erad dos På en a ättstam ha inga tumö er erhåll ts v d långvarig tillförsel Alla utförda mutagen nd rsök inga har ant negativa
Doseri g, förpackni gar och priser Se FASS

KABI

Kabi AB Kabi Läkemedel 112 87 Stockholm

Acta Obstet Gynecol Scand 59 429–431 1980

RESULTS IN THE OPERATIVE TREATMENT OF PELVIC ENDOMETRIOSIS

Jukka Puolakka Antti Kauppila and Lars Rönnberg

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stract Two hundred and eight patients treated surgically endometriosis were reviewed one to four years later The dence of endometriosis in this survey was 17 per cent of gynecological laparotomies After operation 30 per cent he patients were symptomless 60 per cent estimated the vation as good or moderate and only 10 per cent had benefit from the operation In the 32 cases where infer y was the main indication for operation and other fac affecting fertility were excluded 20 pregnancies of 19 nen were achieved *after operation*

incidence of endometriosis is 15 – 25 per cent of gynecological laparotomies (3) and the frequency aid to be increasing with the trend towards smaller ilies (4 5) In spite of new drugs such as synthetic gestagens and danazol surgery will obviously re ı the principal means of treatment especially n severe pain infertility and adnexal mass is pre

In order to get information about the efficiency he different operative methods we analyzed ospectively the patients operated on for en etriosis in our hospital during the years |–76

le I A *Distribution of patients according to age*

	<25	25–29	30–34	35–39	≥40
	12	36	42	42	83
cent	6	17	20	20	40

le I B *Distribution according to parity*

ty	0	1	2	3	≥4
	56	46	47	33	26
cent	27	22	22	16	13

METHOD AND PATIENTS

During the study period the incidence of endometriosis was 17 per cent of all laparotomies or scopies performed in the gynecological department of our hospital Two hundred and eight patients were available for a follow up study one to four years later (mean interval 2 6 years) One hundred and eighty seven patients attended the hospital clinic and were interviewed and examined by one of us Twenty-one patients returned a filled in questionnaire The age of the *patients at the time of the surgery ranged from 20 to 53* years (Table I) Half of the patients were over 35 years Low parity was associated with endometriosis Forty nine per cent were nulligravidae or had one child

The three cardinal symptoms before surgery were dysmenorrhea lower back pain and dyspareunia (Table II) The other common complaints included pain on walking rectal pain nausea infertility and menstrual disorders

On pelvic examination adnexal mass and tenderness were present in 57 per cent of the cases nodularity and tenderness of the pouch of Douglas and uterosacral ligaments in half of the patients and fixed retroverted uterus in 25 per cent

Eighty eight patients had been treated with hormones (synthetic progestagens or estrogen progestagen combina *tion) before surgery In these cases 8 per cent had ex* perienced the response as good while 50 per cent had had no relief

Table II *Percentage of different symptoms 208 pa tients*

	Per cent
Dysmenorrhea	92
severe	76
moderate	16
Low back pain	82
severe	59
moderate	23
Dyspareunia	59
severe	31
moderate	28
Pain on walking	40
Rectal pain	37
Nausea	29
Infertility	29
Menorrhagia	28
Diarrhea	22
Dysuria	17
Fever	17

Table III *Distribution of operations*

	No	Per cent
Radical		
Hysterectomy + bilateral salpingo-oophorectomy	51	25
Hysterectomy + preservation of some ovarian tissue	33	16
Total	84	41
Conservative	124	59
Resection + presacral neurectomy	51	25
Resection	45	22
Electrocoagulation of endometrial implants	4	2
Laparoscopy	19	10
Total	124	59

As assessed during the operation the disease most frequently involved simultaneously the ovaries the pouch of Douglas and the uterosacral ligaments (42 per cent) In one third of the patients only the ovaries were affected

Operative therapy Fifteen patients had been previously operated on for endometriosis Total abdominal hysterectomy and bilateral salpingo oophorectomy with excision of the areas of endometriosis was performed on 51 patients (Table III) In 33 cases using the same procedure some ovarian tissue on the other side was preserved Fifty one patients had conservative surgery which included excision of the areas of endometriosis resection of the ovaries and the uterosacral ligaments and presacral neurectomy with suspension of the uterus Forty five patients had only resection without neurectomy

Of the patients whose age exceeded 39 years 82 per cent had radical surgery For those under 30 only conservative operations were performed

RESULTS

Thirty per cent of the patients were symptomless after operation 41 per cent estimated the overall result as good and 19 per cent as moderate Only 10 per cent experienced deterioration or had no help from the operation Radical surgery resulted in 99 per cent relief of the presenting symptom In the conservative surgery group with neurectomy 90 per cent of the patients had complete or some relief of the actual symptoms When only resection was made a moderate or good result was achieved in 80 per cent of the cases Thus neurectomy improved the result by 10 per cent Dysmenorrhea was present in 191 women before operation and 84 per cent of them had complete or moderate relief of the symptom Lower back pain and dyspareunia were affected in the same manner (Table IV) In 15–24 per cent of the cases the actual symptom was unchanged or aggravated a[illegible]tion

Eighty patients had a trial on progestagen [illegible] after operation (mean duration of treatment [illegible]ths) This did not improve the results.

During the follow up time 17 pa[illegible] (11 per cent) had a recurrence of the disease that [illegible] reoperation They all had had conservative [illegible]

Infertility Infertility was the main indication [illegible] operation in 60 cases In spite of that 8 [illegible] radical surgery because the disease was so e[illegible] The rest of the patients 43 had conservative [illegible]tion or only laparoscopy (9 cases) Co[illegible] location of the endometriosis this group d[illegible] fer from the other patients After exclusion [illegible] other factors affecting fertility (deficient ma[illegible] 9 and use of contraceptives 2 radical surg[illegible]ly laparoscopy 17) a 63 per cent pregnancy rat[illegible] achieved in 32 patients 9 or these 32 women [illegible] preoperative or postoperative progestagen [illegible] them conceived Eleven patients had both pre[illegible]tive and postoperative progestagen thera[illegible] [illegible]cy failed in only 2 cases The rest of the pa[illegible] women had either preoperative or postoper[illegible] mones they had 6 pregnancies The mean [illegible] from the operation to conception was 10 m[illegible] (range 4—24 months) and it was not affected b[illegible] monal therapy These 20 pregnancies of 19 [illegible] ended in normal delivery in 17 cases in early [illegible] in 2 cases and in one legal interruption of p[illegible]

COMMENT

The reported incidence of endometriosis enco[illegible] in pelvic explorations varies from 15 to 25 pe[illegible] (3) though an incidence as high as 40 per ce[illegible]

Table IV *Effect of the operative ther[illegible] different symptoms of endometriosis The re[illegible] given in percentages in parentheses the n[illegible] patients with the symptom before oper[illegible]*

Symptom	Complete relief	Moderate relief	[illegible]
Dysmenorrhea (191)	41	43	[illegible]
Low back pain (171)	44	41	[illegible]
Dyspareunia (125)	53	[illegible]	[illegible]
Pain on walking (53)	54	[illegible]	[illegible]
Rectal pain (77)	54	23	[illegible]
Nausea (60)	53	31	[illegible]
Diarrhea (46)	49	31	[illegible]
Dysuria (35)	51		

ınd recently ın a large serıes by Wılliams (5) In the ısent survey the ıncidence was 17 per cent

Age parıty presentıng symptoms clınical fındıngs d the location of endometriosis ın this study are ın cordance with the results reported earlier (3)

Symptom relief after operation was good ın our pa ıts Similar results have been reported by Garcıa and Williams (5) The best results were achieved th radical surgery When conservative surgery was ployed presacral neurectomy added some 10 per ıt to the good results With hormonal pseudopreg ıcy treatment satisfactory results have been ported ın 84 – 98 per cent of cases (4) In our survey ly half of the patients had satısfactory results from rmonal therapy The disease may have been more ensive ın these patients because they were later ected for operative therapy Andrews (1) reports as h as 68 per cent recurrence of the signs or symp- ns of the disease after pseudopregnancy

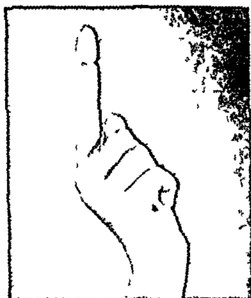
n our study the pregnancy rate was 63 per cent and light ımprovement was noted when the patient had n treated with synthetic progestagens both pre d postoperatively In the series of Andrews (1) a 9 per cent pregnancy rate was reported after gery and 25 8 per cent after pseudopregnancy A nbination of the two treatments resulted ın an even ver pregnancy rate ın Andrews series Our results confirm that surgery still remains the principal thera peutic means for pelvic endometriosis This is especially true when severe pain adnexal mass or in fertility is present

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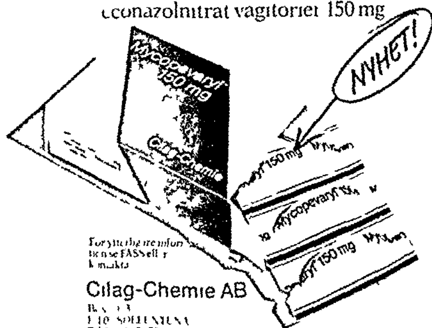


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Acta Obstet Gynecol Scand 59 433–437 1980

URETHRAL PRESSURE PROFILE AT PUBOCOCCYGEAL REPAIR FOR STRESS INCONTINENCE

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tract The influence of pubococcygeal repair on the :ral pressure profile as well as the cure rate technical ative results and side-effects have been studied in 16 rely stress incontinent patients The patients were wed during the first postoperative year in order to t the possible long term effects of devascularization rvation and scarring on the urethral tone Examina using simultaneous urethrocystometry with recording he urethral pressure profile at rest was undertaken peratively 3 months postoperatively and one year operatively Urethral functional length was *not* affected te surgery Urethral closure pressure was slightly reduc months postoperatively and did not recover completely in the first postoperative year Such a reduction in :ral pressure probably reflects damage to the urethral e due to devascularization and denervation Its main cal importance concerns cases of severe stress incon ce with a very low initial closure pressure in the ra. Here vaginal surgery may jeopardize the success of therwise technically ireproachably performed opera On the whole pubococcygeal repair is effective in ning continence although the side effects call for ful selection of patients

ococcygeal repair (4) results in a cure rate of ap ximately 85 per cent in severely stress incontinent ien (7) We know from earlier studies that the ration of continence is not greatly dependent on rovement in urethral tone or pressure at rest even igh efficient support for the urethra has been blished (5) The advantages of good support ath the urethra are only revealed in a stress situa not at rest (3) Unfortunately the surgical pro- ire which involves extensive dissection beneath bladder and the urethra often with abundant ding may damage urethral vascularization and rvation thus reducing tone in the urethral wall as ing and scarring continue postoperatively We studied the influence of pubococcygeal repair on hral pressure during the first postoperative year means of simultaneous urethrocystometry with rding of the urethral pressure profile at rest

MATERIAL AND METHODS

Operative technique An extensive arcuate incision in the introitus is used to get good access to the urethra and the posterior aspect of the bladder (Figs 1 and 2) Extensive ligation of vessels in this area may be necessary The so call ed bladder ligaments are sutured together in the midline elevating the bladder neck sufficiently to obtain continence on provocation such as a cough if the patient is under epidural anesthesia or direct pressure suprapubically if general anesthesia is used (Fig 3) Then both pubococcygeal muscles are cut and their anterior portions are sutured together under the bladder neck and the proximal urethra creating a muscle sling loosely arranged which just prevents excessive downward rotation of the urethra on stress (Figs 4 and 5) The posterior parts of the muscles are attached to the ischiocavernous muscles laterally Finally the bulbocavernous muscles are partly freed and sutured together as a support for the distal urethra without division (Fig 6) Excessive parts of the anterior vaginal wall may be resected and the introital incision is closed A vaginal pack is needed as well as a suprapubic catheter for urinary drainage A coexisting rectocele may or may not be treated at the same time Levator sutures will be somewhat less effi cient since the pubococcygeal parts of the levators have been cut for the creation of the muscle sling The pack is removed after 24 hours and the catheter can usually be removed after 5—8 days

Subjects Sixteen women mean age 57 years (range 31 – 77) and mean parity 2 3 (range 0 – 4) suffering from clinically verified severe stress incontinence who had urinary leakage on moderate exertion such as laughing walking up stairs rising and running No urgency was present and urinary cultures were sterile Cystoscopy was normal No medical treatment had been tried except estrogens a couple of weeks preoperatively in all cases This treatment was discontinued immediately postoperatively Some patients had tried pelvic muscle exercise with poor result

Method Simultaneous urethrocystometry with recording of the urethral pressure profile was performed preoperatively (before estrogen medication) as well as 3 months and 1 year postoperatively The diagnosis of pure severe stress incon tinence without complicating factors had been established and the patients were operated on as described above Post operatively continence was checked and side-effects noted The position of the bladder neck i e the technical result of the operation was evaluated Residual urinary volume was checked at all examinations

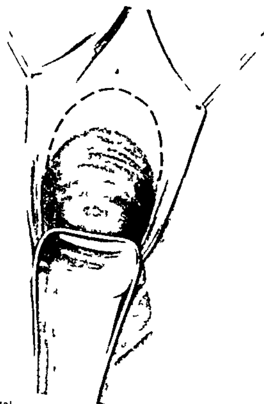


Fig 1 The introital incision

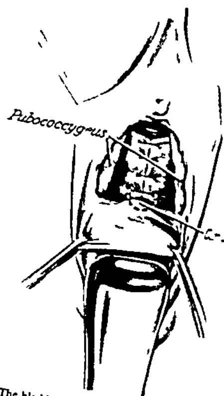


Fig 3 The bladder ligaments sutured in the end

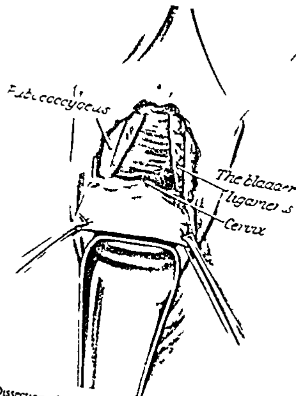


Fig 2 Dissection of the anterior vaginal wall and exposure of the bladder ligaments and the pubococcygeal muscles

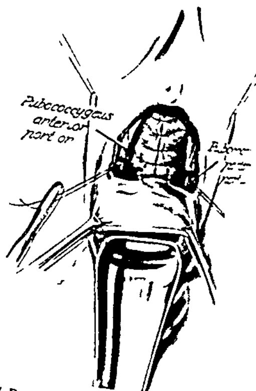
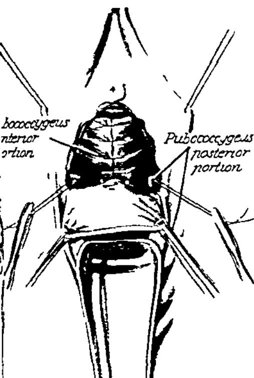


Fig 4 Division of the pubococcygeal muscles



5 The formation of a muscle sling by suturing the rior portions of the pubococcygeal muscles together

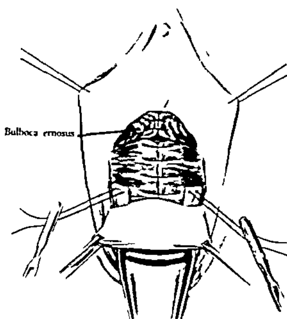


Fig 6 The bulbocavernous muscles sutured together beneath the distal urethra

ie equipment for simultaneous urethrocystometry has described by Asmussen & Ulmsten (1 2) A thin one catheter contains two sensor areas 6 cm apart Via otransducers and amplifiers the urethral pressure the der pressure and the difference between them the iral closure pressure can be recorded The catheter is m through the urethra by an electric motor at constant ity until the proximal sensor has passed the entire ira The distal sensor remains in the bladder Thus the iral pressure profile i e the pressure registered con jously from the internal to the external opening of the ira is recorded The parameters of the urethral sure profile are the functional length the maximum ure and the maximum closure pressure (Fig 7) The nts were examined in the lithotomy position The blad was filled with saline solution at 25 ml/min through a baby feeding catheter After each 100 ml three urethral sure profiles were recorded the third one being used for ons (6) The patients were also asked to hold to test their ability to voluntarily improve urethral re Cystometry was continued till the bladder capacity or until the bladder contained 500 ml

RESULTS

een from Table I there is a marked tendency tow a lower closure pressure 3 months postoperative ly However a statistically significant difference is not a constant finding at all bladder volumes At 300 ml bladder content there was no statistically significant difference between pre and postoperative values otherwise the difference was clear ($p<0\ 05$) One year postoperatively there was still a tendency although less marked with statistically significant differences only at 200 and 400 ml bladder volume ($p<0\ 05$) The functional length of the urethra was unaffected by surgery

Holding urine resulted in an increase in closure pressure in half of the patients preoperatively and in half of the patients postoperatively although not necessarily the same ones

Three months postoperatively 15 patients were cured and one improved The bladder neck was well elevated in all cases and downward rotation on straining was limited One year postoperatively 14 patients were still cured one had a slight degree of stress incontinence and one was as severely stress incontinent as before the operation The bladder neck was still well elevated in all cases

Two women had a persistent residual urinary volume of more than 50 ml Only 5 women were free

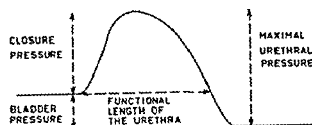


Fig 7 The urethral pressure profile and its parameters

from side-effects or recurrence Major side-effects were protruding rectocele and hypertrophy of the cervix The side effects are listed in Table II

DISCUSSION

It was apparent that pubococcygeal repair did not dramatically alter the shape of the urethral pressure profile at rest which is in accordance with our earlier findings (5) The newly established support for the urethra and the bladder neck did not increase either the functional length or the closure pressure at rest On the contrary there was a strong tendency towards a lowered closure pressure 3 months postoperatively It is likely that the dissection of the anterior vaginal wall with the extensive ligation of vessels which is often necessary may damage urethral tissues and innervation enough to partly destroy urethral tone thereby reducing urethral pressure In stress incontinence any further loss of closure pressure is undesirable especially if the initial closure pressure is al

Table I *Urethral closure pressure and functional length before and after pubococcygeal repair for stress incontinence (n = 16)*

Bladder volume ml	100	200	300	400	500
Mean urethral closure pressure mm Hg					
Before surgery	25 1	[illegible]4 8	[illegible]9	[illegible]4 4	20 3
	(9 65)	(7 98)	(9 34)	(8 30)	(6 20)
3 months after surgery	18 9	17 5	17 1	17 7	14 3
	(6 78)	(7 [illegible]3)	(7 [illegible]2)	(7 31)	(6 20)
1 year after surgery	[illegible]0	18 8	19 3	17 4	16 5
	(5 40)	(5 71)	(6 86)	(6 1[illegible])	(6 [illegible]6)
Mean urethral functional length mm					
Before surgery	[illegible]3 3	[illegible]1	[illegible]0 3	20 1	19 4
	(4 6)	(3 1)	(5 0)	(4 5)	(2.9)
3 months after surgery	[illegible]3 1	[illegible]3	[illegible]1 3	[illegible]0 4	18 7
	([illegible]9)	(3 3)	(3 4)	(4 [illegible])	(3 4)
1 year after surgery	[illegible]3 8	2[illegible]	[illegible]9	[illegible]9	[illegible]3
	(3 1)	(4 5)	([illegible]1)	(4 8)	(5 8)

Standard deviation in parenthesis n 10 n = 1[illegible] n = 15

Table II *The side-effects after pubococcygeal rep[illegible] in the 16 women examined*

Side-effect	N[illegible]
Rectocele	4
Cervical hypertrophy	3
Introital stenosis	1
Urgency	1
Urethral stenosis	1
Coital disturbances	5*
Residual volume (>50 ml)	[illegible]
Great loss of closure pressure	1

out of 10 sexually active † leading to recurrence

ready low Therefore if alternative operat[illegible] niques are available it may be wise not to [illegible] vaginally in cases with a very low preopera[illegible] pressure Otherwise reduction in closure pr[illegible] reduce the usually good result of the oper[illegible] Thus in spite of a well elevated bladder ne[illegible] tient may be as stress incontinent as she was [illegible] beginning This is what happened to the one p[illegible] in our study who one year postoperatively [illegible] improved However the suggestion that the [illegible] approach may result in progressive scarring [illegible] destroying urethral tone could be discarded [illegible] further reduction in closure pressure was [illegible] the immediate postoperative period

In other respects the results agree well [illegible] earlier experience that pubococcygeal repair [illegible] tive in achieving continence the muscle sl[illegible] ing contractile in half of the patients The side[illegible] are multiple Some degree of rectocele pos[illegible] ly is almost unavoidable as a consequence of [illegible] rangement of the levator muscles A prim[illegible] or colporaphy does not prevent the later [illegible] of rectocele (7) Besides it is difficult to [illegible] stable posterior vaginal wall since the lev[illegible] and of little use as support It is possib[illegible] rectocele may be of benefit urodynam[illegible] acts as a bulging support under the ureth[illegible] bladder neck during stress We believe [illegible] be left untreated provided it does not tr[illegible] tient

Cervical elongation and hypertrophy [illegible] cur as a consequence of the bladder [illegible] fixed to the cervical stroma proxima[illegible] tends to be drawn towards the intro[illegible] shrinks

The disorganisation of the vaginal [illegible] pubococcygeal repair may cause co[illegible]

na may have become too wide the introitus too ow sensitivity impaired or intercourse may be iful because of roughen scarred surfaces Accor ly it may be wise to use pubococcygeal repair caution in young and sexually active women

CONCLUSION

ococcygeal repair tends to impair urethral tone reduction in tone may be of importance clinically the initial urethral closure pressure at rest is low preoperatively Otherwise the possible ve effects on the urethral pressure are more compensated by the achieved improvement in ire transmission to the urethra (3)

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RESPONSE OF ENDOMETRIOID OVARIAN CARCINOMA IN NUDE MICE TO THE COMBINATION OF VINCRISTINE SULPHATE AND CYCLOPHOSPHAMIDE

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ract The effect of a combination treatment with vin ne sulphate and cyclophosphamide to endometrioid an carcinoma grown in nude mice hosts was studied by pathological ultrastructural and biochemical methods e first course of treatment had little or no effect After econd and third courses however the growth of the was suppressed as evidenced by increased necrosis decreased weight of tumors The total volume of the chondria decreased but there was no change in the o-cytoplasmic ratio and other ultrastructural features e DNA and RNA contents a decreasing trend was d

complete remission was observed during the treat However in two treated animals kept for a longer va on period the tumors regressed completely and no urr or growths were found In the control animals the rs grew progressively and the histology was identical to n the patient However the frequency of mitoses was ly higher in the transplanted tumor than in the primary r

mple *in vivo* method for the testing of the sen ty of human carcinomas to various antineoplast ents is potentially of great value The human or/nude mice system fulfils a number of criteria useful model in cancer chemotherapeutic studies most important advantage is that a human can can be treated in a living organism in the same as in a cancer patient and it is possible to study ltaneously the correlation between the toxicity the benefit of the treatment in the whole organ In these respects the nude mouse model is superi o any *in vitro* model A variety of human malig tumors can be transplanted to nude mice (11) characteristics of the human donor material are preserved (9)

ndometrioid ovarian cancer is often radiosen e and intrapelvic for a relatively long period (6) ocal recurrences and extrapelvic processes are ver difficult to control Like endometrial car ma it generally shows a relatively poor response to cytostatics However our clinical observations (5) indicate that these tumors in certain cases respond well to the combination of vincristine sulphate and cyclophosphamide Therefore we undertook a study of the effects of this combination *in vivo* in nude mice hosts by histopathological ultrastructural and biochemical methods

MATERIAL AND METHODS

100 seven week-old SPF female nude mice nu/nu BALB-/c/A/BOM (GL Bolmholtgard Ltd Denmark) were used for the studies The animals were kept under strict SPF condition in Makrolon[R] cages at 27±1 C° and a humidity of 55±5 per cent Autoclaved pellet food (Astra EVOS) and *pasteuri ed* water were provided *ad libitum*

The tumor specimen of poorly differentiated endomet roid carcinoma of the ovary was obtained at laparotomy A solid graft which appeared to be active cancer tissue was chosen The tumor tissue was transferred to sterile test tubes containing Dubcos essential medium without antibiotics The tissue tubes were kept at 4 C for less than one hour The tumor tissue was divided into approximately 2 mm cubes One hundred test animals were inoculated subcutaneously with the solid tumor tissue in the right and left flanks After 35 days the treatment was started with 78 successfully transplanted mice

The animals were divided into sixteen experimental groups All test animals received 0 015 mg/kg vincristine sulphate (Oncovin[R] Lilly) and four hours later 10 mg/kg cyclophosphamide (Lääke) intraperitoneally On the second and the third days the cyclophosphamide treatment was repeated and on the fourth day the test animals were given both vincristine and cyclophosphamide Four test groups received second and third courses one and three weeks after the first treatment The control groups received saline at the same time

The weight of the mice and the size of the tumor were determined twice weekly (Fig 3) In the test groups and in the respective controls the samples for examination were taken 4 7 10 and 14 days after the treatment The animals were decapitated and the tumors removed The weight and the size were determined before a piece from each tumor was cut and fixed in neutral formalin embedded in paraffin and

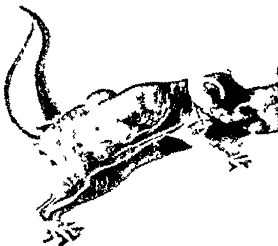


Fig 1 Nude mouse 30 days after subcutaneous inoculation with 2 mm cubes of human endometrioid ovarian carcinoma in the right and left flanks

stained with van Gieson and Hematoxylin Eosin for histological examination Multiple samples from each tumor of the animals decapitated after the third course were taken and processed for electron microscopy as described by Klemi and Grönroos (6) In addition the change in the nucleo cytoplasmic ratio and the total mitochondrial volume of the tumor cells were calculated This was done by measuring the areas of the nuclei cytoplasm and mitochondria in the electronmicrographs with an image analyser (MOB 3 Kontron Meschgeräte GMBH) The rest of the tumor was frozen on CO_2 ice for determination of the DNA and RNA contents The statistical analyses were carried out using Student s t test

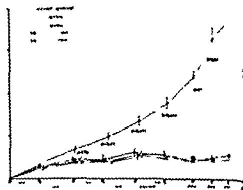


Fig 3 Differences in relative tumour growth in ... treated with three vincristine sulphate cyclophosphamide courses during different periods

RESULTS

The tumors grew fast and had attained a ... size 30 days after inoculation (Fig 1) Twenty ... cent of the animals were eliminated from the ...ment because of unsatisfactory growth of the ... A very low rate of spontaneous mortality was ... during the experiment four animals died in the ...trol groups and two in the treated groups.

In the control groups the size of the tumors ...ed during the experiment to such an extent that ... animal s movements were hampered (Fig 2) ... fore the animals of the last control group were ...itated 10 days before the last treated group

As shown in Fig 3 the relative growth of the ...mors increased progressively in the control g...



Fig 2 Human endometrioid ovarian carcinoma grown subcutaneously in a nude mouse host in the control group 0 days after inoculation with a 2 mm cube of tumour tissue



Fig 4 Human endometrioid ovarian carcinoma ... from a laparotomy H & E ×229



Human endometrioid ovarian carcinoma grown sub ously in a nude mouse for 35 days after inoculation ×260

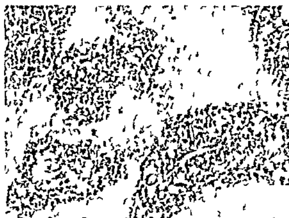


Fig 6 Human endometrioid ovarian carcinoma grown subcutaneously in a nude mouse 14 days after the end of treatment with three courses of combined vincristine sulphate -cyclophosphamide H & E ×184

growth stopped in the treated groups during the l course of treatment and the tumor s size re d almost constant to the end of the experiment ifferences between relative tumor growth in the d and untreated groups were statistically signifi fter the second course of treatment

histology of the primary tumors of the patient ie nude mice was similar with a slightly higher ency of mitosis in the latter The tumor con of solid nests of cells and of glands in loose ctive tissue The epithelial cells of the tumor l in shape and size and contained large nuclei of which were in mitosis (Fig 4 and 5)

effect of the combination therapy was analys itologically after the first and third courses A course did not affect the tumor The tumors of nimals decapitated four days after the third e consisted of solid areas gland and hemor cyst formations surrounded by necrotic tumor Mitotic figures could still be seen in abun The tumors of the animals decapitated on the th day after treatment showed similar histology he necrotic areas were larger In the groups itated 10 and 14 days after the treatment three ers of the tumor tissue were necrotic The viable consisted of small glandular areas and mitotic es could still be seen (Fig 6) No complete remis was observed during the 14 days after treatment ever in two animals which were followed up for nonth after treatment a complete regression of ecrotized tumor was found After this the ani showed no signs of new tumor growth

At the ultrastructural level the cancer cells were elongated or round with irregular and deeply infolded nuclei The cytoplasm contained many mitochondria some profiles of rough endoplasmic reticulum primary and secondary lysosomes and some free ribo-



Fig 7 Low magnification electron micrograph of the endometrioid ovarian carcinoma before treatment At the top of the figure there is seen a lumen of a gland (asterix) One cell is in mitosis (m) Nuclei contain one or two nucleoli In the cytoplasm there are many mitochondria free ribosomes and some profiles of rough endoplasmic reticulum × 6240

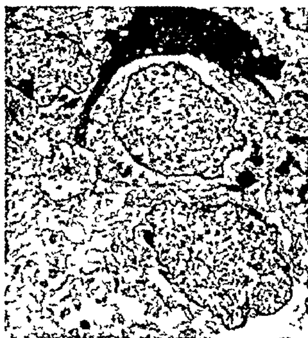


Fig 8 Low magnification electron micrograph of the endometrioid ovarian carcinoma after treatments The tumor still forms glands (asterix) and also otherwise ultrastructurally resembles the untreated one ×6240

somes and polysomes The free surface of the cells was sometimes covered with tubby microvilli and occasionally a cilia was observed Compared with the controls the total volume of the mitochondria decreased ($p<0.001$) but there was no changes in the nucleo-cytoplasmic ratio and other ultrastructural features after the third course (Figs 7 and 8)

The DNA and RNA contents correlated with the macroscopic and microscopic findings The content had a tendency to decrease after treatment The RNA content in mg/g dry weight decreased from 8.5 ± 1.8 (S E) to 5.6 ± 1.2 in the tumors of the test animals decapitated four days after the third course and correspondingly the DNA content from 45.8 ± 3.2 to 38.6 ± 4.9 The differences are not statistically significant they can only be considered indicative as no determinations were made in the 14-day group

DISCUSSION

The results obtained in this study confirm previous reports of successful transplantations of human malignant neoplasms into nude mice (10 8 3) In the present study we showed that transplanted endometrioid ovarian carcinoma is viable in nude mice hosts The karyotype of the neoplasms was [illegible] transplantation but with a slightly [illegible] of mitoses which has also been reported by [illegible] and Detre and Gazet (2) This may be [illegible] that the transplanted tumor grafts [illegible] therefore better vascularized than the [illegible] tumor

In the modern oncologic treatment [illegible] ics are more and more giving place to [illegible] tive combined agents Both endometrial [illegible] and endometrioid ovarian carcinoma have [illegible] practice in certain cases shown a good [illegible] combination of vincristine sulphate and cyclo[illegible] phamide This was true also in this [illegible] study The therapy was intended to [illegible] models as far as possible (7 4) but with [illegible] vals to suite the faster metabolism of mice [illegible] vals between the different courses in our [illegible] experiments may however have been too [illegible] Despite cessation of tumor growth some [illegible] cinoma tissue could still be seen 14 days [illegible] third course of treatment From the [illegible] point of view the changes in the amount of [illegible] and in the volume of mitochondria were good [illegible] for determining the effect of the treatment

This study supports the usefulness of the [illegible] tumor/nude mice model in selective screening of [illegible] anticancer agents or their combinations for [illegible] against this kind of tumors The method may [illegible] be useful for testing new treatment modal[illegible] studies of cancer tissue immunological [illegible] tumor cell kinetic research and studies of the [illegible] nism of action of antineoplastic agents The [illegible] ence from this study suggests that in rou[illegible] time for the entire procedure could be [illegible] approximately one half

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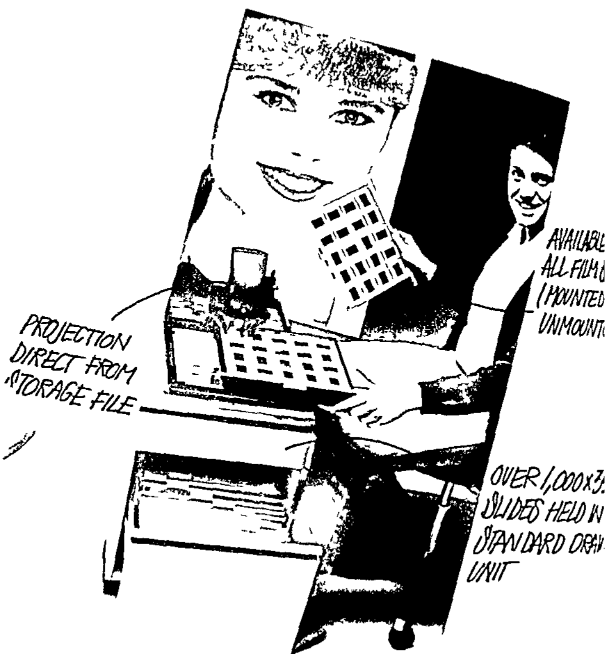
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RADIOIMMUNOASSAY OF hCG AS AN EARLY DIAGNOSIS OF CEREBRAL METASTASES IN CHORIOCARCINOMA PATIENTS

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Abstract To determine the early cerebral involvement of choriocarcinoma the following studies were employed By comparing hCG titers in measurements of serum and cerebrospinal fluid (CSF) hCG-β through radioimmunoassay (RIA) serum/CSF ratios of titers were calculated in patients with normal pregnancies and in those with trophoblastic neoplasia In normal pregnancies the mean ratio of serum/CSF hCG was more than 45 5±6 0 (mean±SEM) 1 In neoplasia without metastases to the brain the ratio was more than 41 0 1 However 2 patients with cerebral choriocarcinoma showed low ratios of 23 0 1 and 20 9 1 respectively This suggests that determination of the β hCG concentration ratio of serum to CSF using RIA might give a more reliable evaluation for the early detection of choriocarcinoma metastasized to the brain

According to Vaughan & Howard (8) cerebral metastasis from chorioepithelioma occurs with an incidence of approximately 20 per cent The highly lethal rate in chorioepithelioma metastasized to the brain is due to hemorrhage and cephalic vessel infarct Therefore it is desirable to find a better way of detecting such metastasis in the earliest possible stage Several techniques such as angiography sonography radioisotope and CT scanning have been employed to determine early cerebral metastases of choriocarcinoma but these examinations have not always been useful for detecting small foci

The purpose of this paper is to evaluate the comparison of human chorionic gonadotropin (hCG) titer in blood serum with that in CSF through RIA of hCG β subunit for the diagnosis of metastasis to central nervous system (CNS)

MATERIAL AND METHODS

Samples for hCG assay were collected from 9 patients with intact hydatidiform mole 8 during treatment after evacuation of hydatidiform mole 4 with destructive mole 5 with choriocarcinoma and 77 normally pregnant women CSF and blood from patients were obtained simultaneously by lumbar puncture and antecubital vein puncture respectively both CSF and blood were stored at -20 C after immediate centrifugation

HCG RIA was done as follows Purified hCG β subunit from Serono Immunochemicals (Italy) was labelled with (Na^{125}I) from the New England Nuclear Corp (Boston Ma USA) by the enzymatic method (1) Specific antisera to the hCG β subunit were provided by the National Institute of Arthritis and Metabolic Disease (USA) Purified hCG (Serono) served as the reference preparation for the assays which were carried out by the double antibody technique described by Vaitukaitis (7) The intra assay variance coefficient was ±8 per cent and the inter assay coefficient ±15 per cent the assay showed a sensitivity of 10 mIU per milliliter

RESULTS

Normal pregnancies HCG concentrations of normally pregnant women were assayed in serum and CSF throughout gestation The mean ratio of hCG titer in serum to that in CSF in the second month of pregnancy was 128 5±13 2 (mean±SEM) 1 representing the highest ratio in all trimesters After this highest value the mean ratio began decreasing to 98 6±1 5 in the third month of pregnancy and to 52 8±4 0 in the fourth month

Because some CSF samples (1 of 5 in the seventh month of pregnancy and 2 of 5 in the ninth month) had undetectable values making the ratio impossible to calculate the mean ratios were greater than 45 5±6 1 in the seventh month (Table I Fig 1)

Molar pregnancies HCG concentrations in 8 of 9 patients with hydatidiform mole showed ratios ranging from 265 6 1 to 455 8 1 while a patient with partial mole showed a ratio of 41 0 1 (Table II)

Although 3 of 8 patients followed up after evacuation of hydatidiform mole showed hCG ratios of 44 8 1 46 0 1 and 50 0 1 respectively the rest had undetectable CSF hCG concentrations All of these 8 continued a benign post molar course

Table I *Normal pregnancies*

Gestational age	No of subjects	Ratio of hCG concentration Serum (M±SE) CFS
II	5	128 5±13 2 1
III	8	98 6±1 5 1
IV	14	52 8±4 0 1
V	11	57 7±5 7 1
VI	3	62 0±12 4 1
VII	5	>45 5±6 0 1
VIII	6	59 1±10 1 1
IX	5	>48 2±7 4 1
X	20	54 5±3 6 1

Destructive moles Four patients diagnosed histologically as destructive mole *in utero* without metastatic lesion showed hCG ratios ranging from 52 1 1 to 310 0 1 These patients entered complete remission following chemotherapy and hysterectomy

Choriocarcinoma Of 5 patients with choriocarcinoma 3 with no evidence of cerebral metastasis—despite electroencephalography cerebral angiography and radionuclide brain scan—showed hCG ratios of 103 2 1 586 7 1 and 251 0 1 respectively

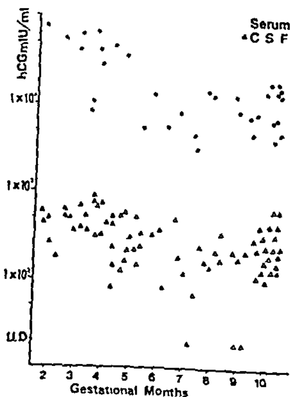


Fig 1 Serum/CSF hCG levels in normal pregnancy

Table II *hCG concentration (mIU/ml)*

	hCG concentration (mIU/ml) Serum CSF	Ratio Serum CSF
Hydatidiform mole		
1	1 333 200 4 380	304 4 1
2	1 000 000 2 400	416 7 1
3	800 000 1 800	444 4 1
4	2 435 000 6 300	[illegible]
5	1 960 000 4 300	[illegible]
6	950 000 2 400	395 8 1
7	425 000 1 600	365 6 1
8	1 000 000 2 700	3 0 4 1
9	41 000 11 000	41.0 1
Post molar pregnancy		
1	1 000 UD	
2	33 600 750	44 8 1
3	330 UD	
4	1 500 UD	
5	9 600 UD	
6	2 300 50	46 0 1
7	UD UD	
8	1 200 24	50 0 1
Destructive mole		
1	13 020 250	52 1 1
2	7 750 140	55 3 1
3	34 100 110	310 0 1
4	62 300 360	173 1 1
Choriocarcinoma		
1	39 200 380	103 2 1
2	70 400 120	586 7 1
3	1 255 000 5 000	251 0 1
4	5 300 230	23 0 1
5	9 600 460	20 9 1

* UD = undetectable

Two patients suspected of having cerebral meta[illegible] showed hCG ratios of 23 0 1 and 20 9 1 respectively

Experiment of hCG transfer from CSF to blood Theoretically if hCG molecules transfer from one compartment to another comparing hCG concentration in one with that in another may not be useful for evaluating the hCG production

To ascertain whether or not a blood-brain barrier exists in the pathway of hCG from CSF to circulatory blood we designed the following experiment A female dog weighing 11 5 kg was maintained under anesthesia using Ketamin with a puncture needle (gauge No 21) set between CII and CIII After confirmed continuous CSF dropping 40 000 IU of hCG suspended with 2 ml of saline was injected into the femoral vein and 0 5 ml of CSF was collected every minutes until 3 hours later

When hCG traces were not detected in any CSF aples a further experiment was developed as fol rs One ml of a solution containing 2 300 000 n/ml of ^{125}I hCG β subunit suspended with a buf was injected into the CSF 0 3 ml of CSF collected minutes later still contained 186 652 cpm/0 1 ml of I β hCG 0 3 ml of CSF collected 3 hours later ntained 49 000 cpm/0 1 ml of β hCG and 0 2 ml (CSF collected 4 hours later contained 26 600 n/0 1 ml of β hCG No isotope content was de ted however in 2 ml of blood collected every 15 nutes until 4 hours later

DISCUSSION

cretc organs involved in 512 cases of choriocar oma reviewed by Park & Lee (3) were as follows g 94 per cent vagina 44 per cent brain 28 per t liver 28 per cent kidney 25 per cent and ry 22 per cent Vaughan & Howard (8) reported t 70 per cent of their chorioepithelioma cases had in metastases Of 92 trophoblastic tumor cases m the Department of Obstetrics and Gynecology kyo Medical Coll ge pulmonary metastases were ind in 55 4 per cent and brain metastases in 13 per t (5) It is particularly difficult to detect early bral metastases of choriocarcinoma before neuro ical signs and cerebral involvement develop even ugh diagnostic methods such as radioactive brain ns cerebral angiography and electroencephalo phy have often been employed

McCormick (2) measured gonadotropin titers in nal fluid using a biological assay of hCG in cases trophoblastic disease By infusing a high concen tion of hCG into a nephrectomized dog he found t the ratio of gonadotropin value in blood to daily ne output and to spinal fluid was approximately 374 1 Tashima *et al* (6) noted that the CSF titer hCG was markedly elevated in confirmed cerebral tastases from choriocarcinoma but they conclud that hCG did not appear in CSF until a high eshold value—equivalent to a urinary excretion of about 250000 IU of hCG/day—had been ex ded Rushworth *et al* (4) measured hCG concen tions in plasma and CSF by RIA in 19 cases of oblastic disease and found that the sma CSF ratios were above 100 1 in most patients hout brain metastases and below 35 1 in patients h intracranial metastases They also proved that hCG concentrations in CSF relative to plasma were especially high in patients whose active tumors were located mainly in the brain or spinal cord

Our study using homologous RIA of ^{125}I hCG β subunit/anti hCG β subunit demonstrated that a ratio of hCG concentration in serum was correlated to that in CSF from the first to the third trimesters of normal pregnancies

Discrepancies in ratios observed in a gestational month might be attributable to (a) changes in spinal fluid volume (b) changes in spinal fluid pressure or (c) changes in permeability

Our experiment with the dog suggested that a blood brain barrier exists between the two compart ments of blood circulation and CSF since the content of hCG infused into circulating blood was not detect ed in CSF until 3 hours later and ^{125}I hCG β subunit infused into spinal fluid had still not transferred to peripheral blood 4 hours later Thus due to the ap- parent existence of a blood brain barrier metastases to the CNS may be diagnosed by calculating the ratio of hCG concentration in serum to that in CSF

In 77 normally pregnant women and in 26 patients with trophoblastic disease serum CSF ratios ranged above 30 1 except for 2 patients with brain metasta ses who showed ratios of 23 1 and 20 9 1 respec tively It therefore seems probable that the critical ratio involving cerebral metastases is below 30 1 in choriocarcinoma patients

Measurement of hCG in CSF may not be necessary to confirm the presence of intracranial metastases and then lumbospinal puncture may be hazardous if increased intracranial pressure is present However occult cerebral metastases are often present without evidence of CNS lesion and therefore the method we have indicated of detecting metastases at an early stage is needed

As mentioned above we should like to emphasize that evaluation of the hCG concentration in a serum CSF ratio is useful for confirming the ex istence of choriocarcinoma in the CNS

ACKNOWLEDGEMENTS

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ENDOMETRIAL EFFECT OF ORAL ESTRIOL TREATMENT IN POSTMENOPAUSAL WOMEN

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stract Estriol is a weak estrogen with a claimed specific ion on the epithelium in cervix uteri and vagina and with or limited ability to induce endometrial proliferation In revious pharmacokinetic study we have shown elevated iol levels *for only 2–3 hours after oral administration* he drug The present study was performed to test if estri when given orally in daily divided doses to postmeno usal women has any effect on the endometrium Twenty tmenopausal women who had no vaginal bleeding in onse to lynestrenol (Orgametil[R] 5 mg×2×V) were ited with 6 mg estriol a day (Ovesterin[R] 2 mg×3) di ed into three doses for 2 up to 3 5 months When lynes iol (5 mg×2×V) was given following the estriol treat nt periods 12 women out of 20 experienced a vaginal eding and one reported spotting Endometrial biopsies in of those women who had a bleeding were examined his gically The endometrium was atrophic in four women liferative in two slightly hyperplastic in one and showed s of weak hormonal activity in one Two women had etory endometrium It is concluded that estriol admin red in a way that gives prolonged elevation of the blood ls is able to produce the same effect on the endometri as other estrogens

e relationship between estrogen replacement thera and endometrial cancer has stimulated interest in riol for the treatment of postmenopausal estrogen ficiency symptoms (1 10 15 19) with its claim of or weak effects on the endometrium and its ascrib specific action on the epithelium of the cervix and gina (2 8)

The rapid conjugation of orally administered estri explains the *short biological effect after a single ad* nistration (14) Despite this estriol is reported to ieve vasomotor symptoms without inducing endo etrial proliferation (18) Estriol is known to bind to man endometrium (17) but a rapid decline in the clear receptor estriol complex has been described er a single dose (3) With repetitive hormone injec ns to rats the potency of estriol is similar to that of radiol with respect to the induction of uterine owth (3)

The present study was performed to examine if estriol when administered orally in daily divided doses had any effect on the endometrium in postmenopausal women

MATERIAL AND METHODS

Postmenopausal women scheduled for surgical treatment of uterine prolapse were enrolled for the study None of them had been on estrogen therapy during the last year To exclude women with a proliferative endometrium lynestrenol (Orgametil[R]) 5 mg was given twice a day for five days The effective oral dose of lynestrenol in the Kaufmann test in climacteric women is 35–70 mg/cycle (12) Eleven women who got a vaginal bleeding after lynestrenol treatment were excluded from the study These women were generally younger than the average for the group studied Twenty women with no withdrawal bleeding were recruited for the study They were 53 to 76 years old and had had their last vaginal bleeding at least one year ago All 20 women got 6 mg estriol (1 mg tablets of Ovesterin[R] Organon) a day orally for a minimum of two and a maximum of 3 5 months Estriol was given in three doses daily (2 mg×3) Immediately after the treatment period all but one woman got lynestrenol in the same way as before estriol treatment started One woman did not complete the study

Dilatation and curettage were performed in 10 out of 12 women who got a withdrawal bleeding after the lynestrenol treatment at the end of the estriol treatment Two women did not collaborate Specimens from the endometria were examined histologically at the Department of Pathology of University Hospital Uppsala

RESULTS

Treatment periods and results in each individual are listed in Table I None of the women had a withdrawal bleeding when lynestrenol was given before the estriol treatment During treatment with estriol three out of 20 women had spotting after two months Spotting was defined as a minimal vaginal bleeding demanding a minimum of sanitary protection

When lynestrenol was given immediately after the estriol treatment period 12 women had a vaginal bleeding one had spotting

Age years	Lynestrenol 5mg×2 w Bleeding	Estriol 2mg 3 Period of treatment (1 2 3 months)	Lynestrenol 5mg 2 w Bleeding	D&C PAD Endometrium
76	–			atrophy
68	–			desquamation secretion
66	–		–	
65	–			slight hyperplasia
64	–		+	proliferation
62	–		–	
62	–		–	
61	–			atrophy
61	–	spotting		
61	–		+	secretion
60	–		–	
60	–		+	atrophy
60	–		+	
58	–	spotting	+	
57	–		–	
57	–		+	atrophy
57	–		–	
56	–		spotting	
54	–		+	proliferation
53	–	spotting	+	weak hormonal activity

Fig 1 Age distribution of subjects treatment periods with lynestrenol (Orgametil[R]) and estriol (Ovesterin[R]) in twenty postmenopausal women *The second lynestrenol treatment period started immediately after the estriol treatment period* No vaginal bleeding is indicated by – vaginal bleeding by + Results of the histological examination of the endometrium in those women who got a vaginal bleeding are given to the right in the figure

Histological examination showed an atrophic endometrium in four women The endometrium was proliferative in two women and slightly hyperplastic in one secretory in one and secretory and desquamating in one

One woman with vaginal bleeding and one with spotting did not accept curettage

DISCUSSION

In the present series of patients the estrogenic effect of estriol on the endometrium was clear The same endometrial changes as induced by estradiol were found

Estriol is a short acting estrogen In a recently completed pharmacokinetic study we have shown that women receiving 6 mg and 12 mg of estriol orally in a single dose showed elevated plasma levels of estriol already after 15 minutes with peak concentrations after 45 minutes in most women the concentration was down to pretreatment levels after 3 hours (5) Recently Schiff *et al* reported that administration of estriol either vaginally or orally resulted in a significant decrease of serum FSH and LH levels (14) In Schiff's study peak levels of unconjugated estriol were measured one hour after vaginal administration The estriol concentration then declined [illegible] ministered estriol was rapidly conjugated [illegible] however some elevation of unconjugated [illegible] minutes after and as late as 4 hours following [illegible] oral dose

The nuclear binding time of estriol [illegible] studied in rats (3 16) The binding time [illegible] only early uterotrophic events are [illegible] true uterine growth To achieve late [illegible] events a minimum of 6 hours of receptor [illegible] required (3 16)

A likely explanation for the estrogenic [illegible] estriol reported in this study is that when estriol [illegible] ministered orally in repetitive daily doses, the [illegible] estriol levels will be elevated for a sustained [illegible] allowing the nuclear receptor to be occupied [illegible] enough to stimulate late uterotrophic events [illegible] cellular proliferation

The classification of estriol as a weak [illegible] probably valid when estriol is administered [illegible] day Tzingounis *et al* (18) administered once a day for six months to postmenopausal [illegible] They found clinical effectiveness on [illegible] stability and vaginal epithelium but failed to [illegible] duction of endometrial proliferation The lack of sensitivity of the endometrium to [illegible] may reflect the schedule of administration [illegible] low doses used

Puck observed that estriol given at 5 mg a day [illegible] days (a total dose of 30 mg) to 5 menopausal [illegible] did not induce withdrawal bleeding and there [illegible] microscopic evidence of endometrial stimulation [illegible]

Haskins *et al* treated 60 women with 1 mg [illegible] *day for 28 days The patients ranged in age from* [illegible] 94 years Three patients showed evidence of [illegible] drawal bleeding following therapy The [illegible] 48 70 and 72 years and they were noted to have [illegible] ulation of the vaginal mucosa at a level [illegible] greater than the mean of the study group [illegible] withdrawal bleeding occurred in one of [illegible] who received megestrol on completion of the [illegible] regimen In two patients the endometrium was [illegible] ined histologically Minimal estrogen [illegible] noted (6)

Recently Myhre reported the outcome of [illegible] treatment in 213 postmenopausal women [illegible] dosage varied from 1 mg/day up to 8 mg [illegible] tients Estriol was given for three weeks [illegible] tion was suspended for three days [illegible] time was between 1 and 3 5 years No [illegible] red when the estriol dose was 2 mg or [illegible]

...en on 3 mg estriol per day experienced bleeding ...ttage revealed an atrophic endometrium in all

...user *et al* (7) found an estrogenic effect on the ...metrium in 39 of 40 postmenopausal women ... estriol succinate was administered orally The ...ge was 2 4 and 8 mg daily for at least 14 and up ... days The degree of stimulation of the endomet... was not a linear function of increased dosage ...luration of treatment However they did not re... whether estriol was administered once or several ... daily

... most studies mentioned above estriol has been ...nistered once a day and/or in small doses Our ...show that daily repetitive oral administration of ...ol is able to induce estrogenic activity in the en...etrium as estradiol

...riol has been claimed to be a noncarcinogenic ... even an anticarcinogenic estrogen (9) and has ... classified as a safe estrogen When single doses ...iven estriol competes with estradiol for nuclear ...ing sites but is dissociated from the receptor be... late uterotrophic events are stimulated (4) When ...inistered in daily repetitive doses resulting in sus...d elevated estriol levels the receptor estriol com...s occupy nuclear retention sites equally well as ...e ptor estradiol complexes late uterotrophic ...s are maximally timulated and there is no an...nism (4)

...conclusion the mode of estriol administration is ...factor that determines whether or not the drug ...have an estrogenic effect on the end organs Our ...indicate that estriol is able to produce the same ...ts on the endometrium as other estrogens if it is ...inistered repetitively resulting in prolonged elev... of the blood levels and continuous stimulation ...e estrogen receptors

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.HE INFLUENCE OF ADRENALECTOMY ON THE BIOMECHANICAL PROPERTIES)F COLLAGENOUS STRUCTURES OF RATS IN THE POST PARTUM PHASE

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ract Pregnancy influences the functional properties of genital and extragenital connective tissues The sex ones induce a major part of these changes but also cor teroids may play a role as their concentration is ted during pregnancy and early post partum The echanical properties of the pubic symphysis muscle on and skin of intact and adrenalectomized rats during first ten days of the post partum phase were in ated For the pubic symphysis and the muscle tendon e intact animals there was a decrease of the stiffness in ly post partum phase followed by a restoration For drenalectomized animals there was no such initial which indicates that relaxation during pregnancy less pronounced However the strength of muscle ns from the adrenalectomized animals was markedly during the post partum phase The stiffness of in from the intact animals was increased in the early artum period. This increase was also found in ectomized animals but here the strength and stiff ere not only restored to the intact level but became er reduced during the post partum period It seems fore that the adrenal glands not only participate in the opment of adaptive changes during pregnancy but play a role in the stabilization of extragenital connec issues in the post partum phase

connective tissues of the female genital tract ge both morphologically and functionally during nancy (5 12) Extragenital collagenous tissues also influenced during pregnancy with respect to nechanical properties (12) The tensile strength of pubic symphysis as well as muscle tendons in the was thus found to be decreased at the end of nancy and during the post partum period The mal contraction of the collagen fiber bundles in ail tendons was increased during the post partum d (12) The mechanism behind these extragenital tions in the collagenous framework is unclear sex hormones probably play a major role The ementioned change in the pubic symphysis can be elicited by a combination of estrogen and in (3 6) However the role of corticosteroids in these reactions should also be investigated as their concentration is elevated during pregnancy and the first 3–5 days post partum (1)

Connective tissues with high metabolic activity are found in the genital tract during pregnancy and post partum as well as in granulation tissues Robertson and Sanborn (11) measured the amount of collagen produced in carrageenan granulomas after treatment with and deprivation of various hormones Estrogen treatment as well as adrenalectomy increased the amount of collagen produced in the granulomas while cortisone treatment reduced it Conversely Jørgensen (7) found no effect associated with adren alectomy on granulation tissue formation nor on con tent of collagen and hexosamines His findings are in agreement with those of Chassin *et al* (2) that adren alectomy did not influence the healing of abdominal incisional wounds during the ten first days The reports on the effects of adrenalectomy are thus con flicting

The present series of experiments was undertaken to study the influence of adrenal corticosteroids on the restorative processes in the connective tissue out side the genital tract during the post partum phase For this purpose the biomechanical properties of ex tragenital connective tissues from intact and adrenalectomized rats during the first ten days of the post partum phase was investigated

MATERIAL AND METHODS

Fifty five Wistar rats divided into groups according to Table I and 150–170 days old when sacrificed were used The animals were mated when in the estrus phase and the day of parturition was recorded All animals were housed under constant conditions with regard to room temperature air humidity and light and had access to food and water ad libitum 0 9 per cent sodium chloride was added to the water given to the adrenalectomized rats Adrenalectomy was per formed 3 weeks prior to the mating and thus 6—7 weeks be

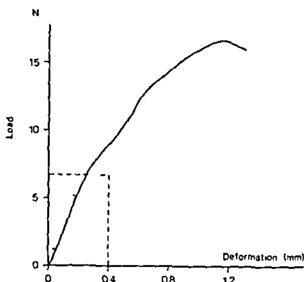


Fig 1 A typical load deformation curve for the pubic sym physis The beginning and end of the linear region is in dicated The part of the diagram as in Fig 2 is marked by broken lines

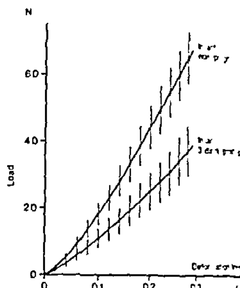


Fig 2 The first part of the mean load-deforma[illegible] for the pubic symphysis from non pregnant a[illegible] partum intact animals
SEM indicated by bars

fore sacrifice The adrenal glands were excised through inci sions in the paravertebral musculature The adrenalectomy technique was checked by determining plasma cor ticosteroids in three adrenalectomized rats which were in jected with corticotropin 10 IU one hour before blood sampling and sacrifice

After sacrifice by means of ether overdosage inspection and microscopic examination confirmed that the adrenal gland sites did not contain any glandular tissue The dorsal skin caudal to the scapular region was removed including the subcutaneous mus le after the hair had been cut close to the skin Standardized 2 mm wide strip specimens were cut at right angles to the longitudinal axis of the animal using a dice with two parallel mounted razor blades The muscle tendons were left in situ in the exarticulated hind limbs under intact skin The tendon of the peroneus long[illegible] was dissected out immediately before tes[illegible] The[illegible] and skin specimens were mounted into two [illegible] clamps with the free distance between them be[illegible] During testing the tendon specimens were [illegible] Ringer s solution (buffered to pH 7 4) at room te[illegible]

The coxal bones were dissected free and the spe[illegible] consisting of the pubic symphysis and the two coxal was wrapped in saline moistened gauze and [illegible] more than one hour when not tested immedia[illegible] The bones were mounted into clamps which [illegible] shaped for the external surfaces of the bone[illegible] specimen was fixed against each clamp with a [illegible] with polyethylene tubing

Table I *Body weights (mean value±SEM)*

Group	Number	Weight gram
Intact		
Non pregnant	8	248±13
Post partum		
3 days	7	275±13
5 days	6	300±16
10 days	7	294±11
Adrenalectomized		
Non pregnant	6	255±15
Post partum		
3 days	6	297±22†
5 days	7	280±30†
10 days	8	289±24†

2 p<0 05 against intact non-pregnant
† p<0 05 against adrenalectomized non pregnant

Table II *Biomechanical properties of the p[illegible] physis (mean±SEM)*

Group	ΔlFmax (mm)	Fmax (N)	[illegible]
Intact			
Non pregnant	1 18 0 14	15 6 1 9	[illegible]
Post partum			
3 days	1 76 0 34	14 0 0	[illegible]
5 days	1 78±0 79	17 5 0 8	[illegible]
10 days	0 93±0 36	13.3 0 6	[illegible]
Adrenalectomized			
Non pregnant	1 [illegible]4±0 [illegible]4	13 8 1 0	[illegible]
Post partum			
3 days	1 5 ±0.23	14 0 0 6	[illegible]
5 days	1 49±0 18	14 1 0 4	[illegible]
10 days	1 46±0 15	12 4 0 8	[illegible]

2 p<0 05 against intact non-pregnant

ble III *Amount of collagen per unit specimen* gth *(mean value±SEM)*

up	No	Muscle tendon mg/mm	Skin mg/mm
ct			
n-pregnant	8	0 108±0 008	0 431±0 016
t partum			
days	7	0 122±0 009	0 437±0 030
days	6	0 124±0 006	0 427±0 026
0 days	7	0 107±0 010	0 449±0 032
renalectomized			
n-pregnant	6	0 129±0 015	0 463±0 021
t partum			
days	6	0 1.4._0 006	0 433±0 015
days	7	0 125±0 011	0 501±0 033
0 days	7	0 143±0 005	0 491±0 020

he materials testing machine (Alwetron T 250) was used constant deformation speed of 2 mm/min and the imens tested until failure The load and deformation sducers were coupled to measuring bridges (Lorentzen fettre) and the signals recorded as a continuous X Y ph on a Hewlett Packard Mosely 7004 recorder For the ic symphysis load-deformation data were read into a wlett Packard 9830A calculator Mean curves and the rdinates for the point of maximum load ΔF_{max} and were calculated The stiffness was estimated as the ent of the angle between the linear region of the curve the X axis tan α These data for the symphysis were further transformed as it is geometrically as well as turally complex A typical load-deformation curve of pubic symphysis is shown in Fig 1 For the curves from on and skin specimens coordinates for every strain in ent of 0 01 were read and the load-deformation data transformed to stress strain Stress values were ulated from load data using amount of collagen per unit imen length as functional cross section area σ_{max} is maximum stress value i e the ultimate tensile gth The deformation values were expressed in units of original length i e as strain $\varepsilon_{\sigma max}$ is the strain value at point of maximum stress The stress strain curve plotted out from these transformed data on Hewlett kard 9862A as shown in Figs 3 and 4

he collagen contents of the tendon and skin specimens e calculated according to Neuman & Logan (8) from hydroxyproline content determined according to the hod described by Grant (4) on a Technicon autolyzer

or each group mean values and standard errors of the n for the different parameters were calculated on the s of the mean values for the tests on each animal in the up The F max test (13) was employed to verify the logeneity of variances and the t test according to dent Newman Keul was used to test the differences be n the groups Differences were considered significant n $p<0.05$

RESULTS

The pregnancies came to full term in all animals without complications The fetuses from the adrenal ectomized animals were generally smaller when com pared to those from the intact ones

No differences were found between the body weights of intact and adrenalectomized non pregnant rats (Table I) Of the intact animals those in the post partum groups had higher weights than those in the non pregnant one The adrenalectomized groups showed the same pattern the weights in the post partum ones being higher

There were no significant differences in the bio-mechanical data on the pubic symphysis (Table II) between intact and adrenalectomized non pregnant groups In the intact group for the third post partum day the elastic stiffness had decreased from the non pregnant state and the first part of the load-deformation curves the toe part became lower (Fig 2) However data from the fifth and tenth post partum days showed a successive restoration The adrenalectomized rats underwent no such change

The amount of collagen per unit specimen length in the muscle tendons differed in none of the intact nor adrenalectomized post partum groups from the corresponding non pregnant groups neither was the amount of collagen in skin changed (Table III)

The biomechanical properties of the muscle tendons in non pregnant rats were not changed by adrenalectomy (Table IV) For the intact rats the elastic stiffness was decreased on the third day of the post partum period and subsequently restored to the level

Table IV *Biomechanical properties of peroneus longus muscle tendon (mean±SEM)*

Group	$\varepsilon_{\sigma max}$ ( )	σ_{max} (N/mg/mm)	tan α (N/mg/mm)
Intact			
Non pregnant	0 24±0 02	158±23	1 020±68
Post partum			
3 days	0 24±0 02	123±12	828±48
5 days	0 21±0 02	117±11	901±49
10 days	0 25±0 03	140±12	955±119
Adrenalectomized			
Non pregnant	0 24±0 01	128±13	851±97
Post partum			
3 days	0 27±0 03	131±19	846±92
5 days	0 26±0 03	125±25	766±65
10 days	0 23±0 02	84±9†	666±87

2 $p<0.05$ against intact non pregnant
† $p<0.05$ against adrenalectomized non pregnant

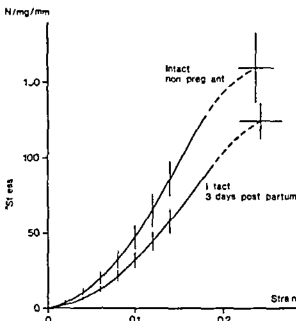


Fig 3 Mean stress strain curves for muscle tendons from non pregnant and 3 days post partum intact animals SEM indicated by bars

found in non pregnant animals The stress strain curves for the intact non pregnant and third post partum day groups are shown in Fig 3 No decrease occurred in the adrenalectomized animals Here however the maximum 'stress' was lower on the tenth day than in the corresponding non pregnant group

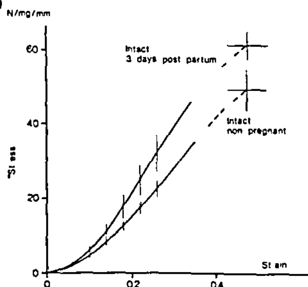


Fig 4 Mean stress strain curves for skin from non pregnant and 3 days post partum intact animals SEM indicated by bars

Table V *Biomechanical properties of the* [illegible] *specimens (mean±SEM)*

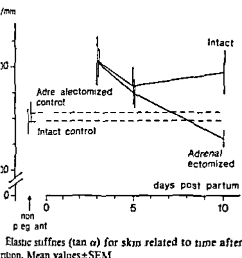
Group	$\varepsilon_{\sigma max}$ (–)	σ_{max} [illegible]	[illegible]
Intact			
Non pregnant	0 47±0 04	49 6 5 3	[illegible]
Post partum			
3 days	0 47±0 04	61 4 3 7	[illegible]
5 days	0 46±0 02	54 5±3 7	[illegible]
10 days	0 46±0 04	[illegible] 5 3	[illegible]
Adrenalectomized			
Non pregnant	0 46±0 04	49 0 5 5	[illegible]
Post partum			
3 days	0 4[illegible]±0 05	55 3 6 8	[illegible]
5 days	0 47±0 03	54 4 4 2	[illegible]
10 days	0 42±0 03	36 8 [illegible]	[illegible]

2 p<0 05 against intact non pregnant
† 2 p<0 05 against adrenalectomized non pregnant
†† 2 p<0 01 against adrenalectomized non-pregnant

For skin there was found with regard to [illegible] biomechanical parameters no differences be[illegible] the intact and adrenalectomized non pregnant [illegible] (Table V) For the intact groups the elastic [illegible] was found to be increased on the third day after [illegible] turition compared with the non pregnant [illegible] 4) In the adrenalectomized rats the [illegible] 'stress' and elastic stiffness were reduced [illegible] tenth post partum day compared to the non pregnant rats These changes in the elastic stiffness during [illegible] post partum period are shown in Fig 5 [illegible] the elastic stiffness was increased on the [illegible] post partum and remained above the level of the [illegible] pregnant state In adrenalectomized rats the [illegible] stiffness was increased on the third day post [illegible] but was subsequently reduced to below the level [illegible] the non pregnant state on the tenth day

DISCUSSION

Pregnancy influences the functional properties of [illegible] collagenous frameworks of the body [illegible] those in the genital tract but also those of the [illegible] tragenital tissues (5 12) In the rat these [illegible] the pubic symphysis were found by [illegible] be a decrease of elastic stiffness while for [illegible] dons there was a decrease of tensile strength [illegible] sile strength of the dermis was found to be [illegible] during the first and second post part[illegible] the post partum period restoration [illegible]



Elastic stiffnes (tan α) for skin related to time after rition. Mean values±SEM

e original state in four to five weeks These fin are *confirmed in the present study* For the hysis and muscle tendons of intact animals in early post partum phase there was a decrease of ic stiffness followed by a restoration as an ated For the adrenalectomized animals how there was no such initial decrease which in es that relaxation during pregnancy had been h less pronounced or absent The strength of the cle tendons in these animals however was tedly decreased during the post partum The skin e intact animals had increased elastic stiffness in early post partum period This reaction was also d in the adrenalectomized animals but here the ngth and stiffness of the skin post partum was not restored to the intact level but became further ced on the 10th day after parturition During the 3–5 days of *the post partum period the concen* on of *corticosteroids is increased (1)* it might efore be suggested that the adrenal glands play a in the stabilization of extragenital collagen in the partum phase when large amounts of collagen e genital tract are catabolized

orticosteroids and corticotropin increase the hanical strength of skin (9 15) Adrenalectomy he other hand has been reported to decrease ten strength of skin during the first 15 post operative s (15) However in this time period the operation uch may influence the connective tissue (10 14) ernal incisional wound results in a decrease of the tic stiffness of skin and also of the denaturing perature of collagen distant to the wound site

The thermal contraction force of the rat tail tendons decreases after an incisional wound but returns to normal three weeks later It is therefore difficult to *differentiate between the influences of the operation* and the lost adrenal function in the first two weeks after the adrenalectomy In order to counter any such phenomena the rats in the present study were there fore adrenalectomized six to seven weeks before the mechanical testing Here the biomechanical data for the intact and adrenalectomized non pregnant groups did not differ from each other

It seems that the adrenal glands do not only par ticipate in the restoration of the mechanical proper ties of the pubic symphysis muscle tendons and skin in the post partum period but they also play a role in the development of adaptive changes like the relaxa tion of the pubic symphysis during pregnancy

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CASE REPORT

MONOZYGOTIC TWINS WITH DISSIMILAR PHENOTYPES AND CHROMOSOME COMPLEMENTS

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stract A case history of monozygotic twins is presented in A showed gonadal dysgenesis and chromosomal saicism (45,X0/46,XX) Twin B was a phenotypical nor l female with the karyotype 46,XX Fifteen previous re rts of monozygotic twins with gonadal dysgenesis are re wed Dissimilar phenotypes seem to be the rule rather in the exception, and mosaicism is found in the majority cases with dissimilar phenotype The assumption is made t the chromosome disorder leading to gonadal dysgenesis ses postzygotically either before or after the process ding to twinning

monozygotic twins dissimilar phenotypes are ex ptional Twelve cases are listed by Nielsen (8) In e cases one twin had Down s syndrome while the her was normal In the remaining seven cases one in had Turner s syndrome while the other was nor l. As the incidence of Turner s syndrome is less an one out of 2 500 newborns and that of mono- gotic twins with female phenotype one out of 0–800 newborns the combination of these two nditions should be anticipated in one out of 1 5–2 llion newborns (12) It is our aim to report a new se and to review the previous 15 reports of mono- gotic twins with gonadal dysgenesis

CASE REPORT

16-year-old patient was referred to our department for rther evaluation of primary amenorrhea Both parents d a sister two years older were healthy The mother had en 35 years old when she became pregnant again The egnancy was uneventful, and the delivery took place at me We have little information about the delivery but it kno n that the patient was born as twin A

Twin A was always smaller than her twin sister but other se she developed normally until puberty When admitted r height was 137 cm and her weight 38 8 kg The neck was ort, but there was no webbing The breasts were not developed the external genitalia were infantile and no axil lary or pubi hair was seen In contrast her twin sister was 162 cm high had a normal female appearance and had menstruated regularly since the age of 13 years Fig 1 shows the twin sisters when they were 18 years old

Hormonal investigations in twin A showed that the urinary excretion of total estrogens was $< 2\ \mu g/24$ h determined by the method of Brown *et al* (1) while the urinary excretion of total gonadotropins was 76–150 mouse uterine units/24 h determined by the method of Johnsen (4) Both thyroid and adrenal function was normal

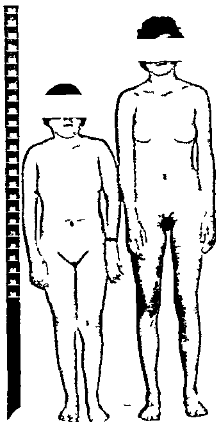


Fig 1 Twins A and B when 18 years old

Table I *Cytogenetic studies of twins A and B*

Subject	Buccal smear: Number of chromatin pos cells	Buccal smear: Number of cells counted	Lymphocytes in peripheral blood: Modal number 43	44	45	46	47	Lymphocytes in peripheral blood: Number of cells examined	Skin: Modal number 43 44 45 46 47	Skin: Number of cells examined
Twin A	a 5	100			9	21		30	5 25	30
	b 2	100			9	20	1	30		
Twin B	17	100	1	1		18		20	not examined	

X rays of the right hand showed that the bone age was retarded by 3 years while X rays of the skull chest and kidneys were all normal

An exploratory laparotomy revealed a hypoplastic uterus and typical streak gonads The streaks were removed and histological examination showed fibrotic tissue without any fol icles

Cytogenetic studies The results are shown in Table I In twin A both a buccal smear and lymphocytes from peripheral blood were examined twice (a and b) The cells with the modal number 46 had a normal female sex chromosome complement whereas the cells with the modal number 45 had an X0 complement Analysis of cells with modal numbers differing from these suggested that they were artefacts during preparation It is concluded that twin A is a 45 X0/46 XX mosaic and twin B a chromosomally normal female

Zygosity studies Determination of erythrocyte phenotypes and tissue types of both twins and their parents was per formed The twins had identical blood groups (Table II)

The probability of monozygosity based on the blood groups is 99 37 per cent according to the method described by Smith & Penrose (15) Furthermore a full thickness skin graft experiment taking skin from twin A and grafting it onto twin B and vice versa was carried out Both grafts ~d a complete take and no rejection occurred during an observation period of 8 weeks This indicates a perma nent survival as could be anticipated in monozygotic twins

DISCUSSION

Until now 16 cases have been reported of monozyg ic twins in whom one or both twins had gonadal dys genesis and a 45 X0 karyotype at least in som Reviewing these cases (Table III) we found 4 w identical phenotype and gonadal dysgenesis in b twins Including our own case 12 cases had d phenotypes In 11 of these cases one twin h gonadal dysgenesis while the other twin in was a phenotypical normal female and in 4 cas phenotypical normal male In one case reported Russell *et al* (12) one twin had gonadal dysge while the other twin showed male intersex one gonad was an immature testis and the o streak ovary Edwards *et al* (3) report a case w one of the monozygotic twins had gonadal dysge *and the karyotype 46 XY/45 X0 in blood and* in skin The other twin was a phenotypical n male with the karyotype 45 X0 in both blood skin no 46 XY cells could be demonstrated Th investigators draw the conclusion that the c available for culture were not necessarily represen tive of those determining the difference in phen

Table II *Erythrocyte phenotypes and tissue types of twins A and B and their parents*

Subject	Blood types: ABO	Rh	MNS	P_1	Lu^a	kk	Le^a	Le^b	Fy^a	Fy^b	Xg^a	Tissue types	
Twin A	A_1	R_1R_1	MNS	+	−	− +	+	−	−	+	+	A_1MNS+s+	C+CW−D+E−c−P I ... Hp 2 1 Gc 2 1 Gc ... PGM 1 1 SP B AK 1 1 PGD A ADA 1 1
Twin B	A_1	R_1R_1	MNS	+	−	− +	+	−	−	+	+	A_1MNS+s+	C+CW−D+E−c−P I ... Hp 1 Gc 1 Gc ... PGM 1 1 SP B AK 1 1 PGD A ADA 1 1
Mother	A_1B	R_1r	MNS	+	−	− +	−	+	+	+	+	A_1BMS+s+	C+CW−D E−c+P+I ... Hp ? Gc 1 1 Gc ... PGM 1 1 SP B AK 1 1 PGD AB ADA 1 1
Father	A_1	R_1r	MNS	+	−	+ +	−	+	−	+	−	A_1MNS+s+	C+CW−D+E−c P+I ... Hp 1 Gc 2 1 Gc ... PGM 1 1 SP B AK 1 1 PGD A ADA 1 1

Table III *Review of 16 cases of monozygotic twins with gonadal dysgenesis*

Reference	Karyotype Blood	Skin	Gonads	Other	Phenotype
Turner & Zanartu	45 X0	45 X0			Turner s syndrome
1956	45 X0	45 X0			Turner s syndrome
Smith & Smith	45 X0				Turner s syndrome
1963	45 X0				Turner s syndrome
Decourt *et al*	45 X0				Turner s syndrome
1964	45 X0				Turner s syndrome
Beekhof *et al*	45 X0	45 X0			Turner s syndrome
1972	45 X0	45 X0			Turner s syndrome
Turpin *et al*				45 X0	Turner s syndrome
1961				46 XY	normal male
Mikkelsen *et al*	46 XX/45 X0	46 XX/45 X0			normal female
1963	46 XX/45 X0	46 XX/45 X0			Turner s syndrome
Edwards *et al*	46 XY/45 X0	45 X0			Turner s syndrome
1966	45 X0	45 X0			normal male
	46 XX/45 X0				normal female
	46 XX/45 X0				Turner s syndrome
Russell *et al*	45 X0	45 X0			Turner s syndrome
1966	45 X0	46 XY/45 X0	46 XY/45 X0		male intersexuality
Maine & Cornery	46 XX				normal female (Xga pos)
1966	–				female with multiple abnormalities (Xga neg)
Moss *et al*	47 XXX/45 X0	47 XXX/45 X0			Turner s syndrome
1969	47 XXX/45 X0	47 XXX/45 X0			normal female
Potter & Taitz	46 XX/45 X0	45 X0			Turner s syndrome
1972	46 XX/45 X0	46 XX			normal female
Chrubina *et al*	46 XX/45 X0				normal female
1975	46 XX/45 X0				Turner s syndrome
Karp *et al*	46 XY				normal male
1975	46 XY		45 X0	46 XY/45 X0	Turner s syndrome
Schmidt *et al*	46 XY	45 X0	45 X0		Turner s syndrome
1976	46 XY				normal male
Present report	46 XX/45 X0	45 X0			Turner s syndrome
	46 XX				normal female

In the four cases with identical phenotype no mosaicism was found In 10 of the twelve cases with dissimilar phenotype mosaicism was found in one or both twins Since mosaicism was present in most monozygotic twins with gonadal dysgenesis both twinning and chromosomal disorder must be postzygotic events

In the present case mosaicism was only found in one twin with gonadal dysgenesis If this is true it seems that twinning took place before the chromosomal disorder leading to the gonadal dysgenesis Another possible explanation is that both twins are mosaics but that the mosaicism in twin B remained undetected because only the blood was examined

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CASE REPORT

ANTENATAL ULTRASONIC DIAGNOSIS OF COMPLETE URETHRAL OBSTRUCTION IN THE FETUS

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A case of ante natal diagnosis of complete truction of the urethra is reported By repeated ultra k B-scans a distended bladder filling the abdominal ty could be seen and a hydroureter was demonstrated early diagnosis of this condition which is incompatible 1 life a decision to terminate pregnancy can be made

fetal urinary bladder should be given special at tion during routine ultrasound scanning as its e of filling can help the examiner to detect dif ent fetal malformations (1 3) Complete obstruc 1 of the urethra is a very rare condition and it ses severe distention of the urinary bladder teral hydroureter and hydronephrosis with con itant oligo-amnios

Three cases of such a malformation detected by rasonographic B-scan have appeared in the litera e two of them were diagnosed antenatally and in third case the final diagnosis was established only r delivery Garret *et al* (2) described two cases one with a complete obstruction and a stillborn is while the other had only a partial stricture lowed by a live birth Okulski (6) reports on a thral obstruction in the fetus with a prune belly drome but the degree of obstruction is not clear e infant died at the age of two months In Nevin s ort (5) an absence of the urethra was found with extremely distended bladder and other malforma ns in different organs The infant died at birth A case of complete obstruction of the urethra is orted here stressing the importance of the possi ity of early detection of such malformations

CASE REPORT

Jewish Yemenite woman aged 25 was referred to the h risk pregnancy clinic when 25 weeks pregnant (accor to the LMP) as the clinical impression was that the tus was larger than expected for the gestational age In the past she had had a spontaneous abortion and a normal delivery of a healthy infant All general laboratory and physical examinations were normal A grey scale ultrasound B-scan revealed a biparietal diameter (BPD) of 54 mm cor responding to 21 weeks of pregnancy no amniotic fluid and a highly distended bladder filling almost the whole fe tal abdominal cavity The intestines were packed tightly towards the spine and the diaphragm and some fluid was seen in the pleural cavity (Fig 1) An attempted amnio-graphy failed as no amniotic fluid could be withdrawn Re peated scans showed the same huge urinary bladder (Fig 2) At 28 weeks s amenorrhea an additional distended body was seen which was assumed to be a hydroureter (Fig 3) With the progress of the pregnancy the picture of intra uterine growth retardation became more evident at 35 weeks the BPD corresponded to 30 weeks Urinary estriol and non stress cardiotocography revealed nothing abnor mal but fetal movements as reported by the patient de creased At 36 weeks after spontaneous labor the patient delivered a male fetus weighing 2 200 g through a partial breech extraction which died a few minutes after birth Physical examination revealed a much enlarged abdomen severe dehydration and a face which was reminiscent of the Potter syndrome Post mortem examination (Fig 4) showed



Fig 1 Longitudinal ultrasonic scan at 25 weeks with di ten sion of the fetal bladder and oligo-amnios H = head B = bladder X = xyphoid area of mother S = symphysis pubis of mother





Fig 2 Longitudinal ultrasonic an of the fetal trunk (regu lar and magnified) Intestines packed backwards and upwards B = bladder D = *diaphragm* I = intestines L = lungs P = pla enta S = maternal symphysis pubis X = maternal xyphoid



Fig 4 Anatomical preparation of the fetal urin with a large bladder and bilateral hyd oureter an phrosis B = bladder U = ureter K = kid ey



Fig 3 Transverse ultrasonic scan of the fetal upper abdomen with a hughe bladder and probable hydroureter B = bladder K = ureter I = intestines L = left R = right

a distended urinary bladder total s enosis of the branaceous part of the urethra part al s enosis of the part of the left ureter due to mucosal valve f partial stenosis of the lower part of the righ ureter at the uretero vesical junction There was bila teral hy rosis with atrophy of the renal parenchyma

DISCUSSION

In the Potter syndrome with bila eral agenesis of the kidneys the ultrasonic ante na al diagnosis is based on unrecognizable fetal kidneys a d bladder oligo-amnios and failure to demo strate the bladder after administration of furosemide to the mother (4) There is also intrau ter growth retardation In the syndrome of complete obstruction of the urethra the diagnosis is made by of

e distension of the bladder which may fill the hole abdominal cavity and sometimes hydroneph s

This malformation causes severe secondary anges in the urinary tract incompatible with post tal life and interruption of pregnancy should be nsidered when the diagnosis is confirmed by ultra-und. In this case the pregnancy was allowed to ntinue as owing to the lack of previous knowledge e obstetricians were not absolutely certain of the di nosis With the description given in this report it is be hoped that more accurate diagnosis will allow early decision to terminate such hopeless pregnan s

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FÖRLOSSNINGSSTOLE

Obstetrikens historia Vi finner det i gamla skrif ter Vi ser det illustrerad på gamla vaser reliefer och kopparstick Fodande kvinnor som sitter på huk står knabojda står eller sitter To m i gamla egyptiska papyrusrullar finns speciella hieroglyfer som framstal ler kvinnor i sittande stallning vid forlossning I 2 a Mosebok 116 kap omnamns en forlossningsstol och vi har en ingående beskrivning av en sådan från Soranus från Ephesus som var forlossningslakare hos den romerske kejsaren år 2 e Kr



Fran Egypten till Europa Forlossningsstolen kom troligtvis från Egypten via romarna till det ovriga Europa Nar boktryckarkonsten hade uppfunnits tryck tes larobocker på olika europeiska språk och då fick vi en rad olika typer av forlossningsstolar På 1700 talet gick forlossningshjalpen mer och mer ... lakarvetenskapen och darmed blev det också vanligare att kvinnan låg under forlossningen Under ... senaste 200 ... har detta varit den vanliga forlossningsstallningen i vår del av varlden Men ... dagar finner ... i folkgrupper som sitter på huk och foder

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Hecon

CASE REPORT

PAPILLARY CYSTADENOFIBROMA OF THE ENDOMETRIUM

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...ract Six cases of papillary cystadenofibroma of the en... ...etrium were found in the medical literature A seventh ... of this kind of tumor is now described clinico-... ...ologically and the literature pertinent to this particular ... of tumor reviewed

... eponym Papillary Adenofibroma (1) ...hasizes a tumor having a fibroepithelial nature ... resemblance to similar growth in the ovary and ...st The first cases of papillary adenofibroma of ...cervical origin were reported in 1971 by Abell ... Eleven reported cases of such tumors in the ...us (1 3 7 8) 5 of them arising from the cervix ...) and 6 from the endometrium (3 7 8) are to be ...d in the medical literature Because of the ...acteristic feature of this kind of tumor having ...nly papillary structures protruding into cystic ...es Grimalt (3) recommended the term papillary ... adenofibroma

... seventh case of papillary cystadenofibroma of ... endometrium the largest in this site hitherto ...nd was considered worthwhile reporting

CASE REPORT

...., a 71 year-old nulliparous widow complained of a ...d-tinged vaginal discharge Pelvic examination revealed ... myomatous uterus the size of a 12 week pregnancy ... cervix was effaced and dilated to 1 cm by the lower pole ... an ebony-colored granular elastic tumor A total ab-...minal hysterectomy and bilateral salpingo-oophorectomy ... performed after biopsy of the mass had revealed a ...eglandular tumor Recovery was uneventful and the ...ient was discharged on the 7th postoperative day ...alf a year after the operation the patient feels well and ... no complaints

...roscopic findings An enlarged uterus (size 16 × 10 × 7 ...) together with adnexae were received for examination The uterine cavity was entirely filled by a tumor which protruded into the external cervical os (Fig 1) The tumor itself was polypoid measuring 14 × 8 × 5 cm and was attached by a broad base to the uterine fundus Its surface was irregular having many round and ovoid nodules On its cut surface the tumor had a spongy consistency and contained mucoid fluid within multiple cystic cavities measuring 0 1 – 1 5 cm in diameter (Fig 2) The uterine wall was 1 5 cm thick with atrophic endometrium covering the tumor free parts On its left lateral wall a spongy sessile polyp was found 3 cm in diameter not contiguous with the larger polypoid tumor The Fallopian tubes and ovaries were quite normal

Microscopic findings Both fibrotic stroma and epithelium were present in the polypoid tumor Cysts and glands of varying size and shape were seen embedded in a fibroblastic stroma throughout the entire specimen Blunt papillary folds protruding into cystic spaces were a general characteristic feature of the tumor (Fig 3) Tall columnar and cuboidal epithelium resembling endocervix lined most of the cystic cavities glands and papillary projections (Fig 4 and inset) This epithelium was flattened in the larger cysts Large amounts of mucicarminophil material was present in the cytoplasm of the lining epithelium and in luminae of the

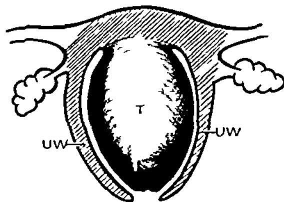


Fig 1 Schematic sketch of specimen before incision UW uterine wall T tumor



Fig 2 Gross appearance of the resected specimen Left side a polypoid mass attached by a broad base to the fundus of the uterus *Right side* cross section shows many cystic spaces variable in size giving a spongy appearance to the tumor



Fig 4 Papillary fold composed of loosely [illegible] fibroblasts covered by columnar [illegible] and eosin ×250
(Inset) Higher magnification Tall [illegible] secreting surface epithelium Hematoxylin and [illegible] ×360

glandular and cystic spaces A few glands and cysts lined by endometrial epithelium were observed in the area where myo and endometrium were contiguous with the polypoid neoplasm The outer surface of the tumor was covered with the same endocervical epithelium In most areas the fibrous stroma adjacent to the epithelium of these structures was composed of small loosely arranged fibroblasts while more compound spindle and stellate fibroblasts made up the deeper cullular region (Fig 3) The nuclei of the stromal cells were uniform and small demonstrating in some places storriform whirled patterns In other areas the cells were hyperchromatic with vesicular nuclei of irregular size and shape having single or multiple nucleoli characteristic of nuclear atypia (Fig 5 and inset) The small separate sessile polyp on the uterine wall had a similar microscopic appearance The endometrium demonstrated senile cystic atrophy

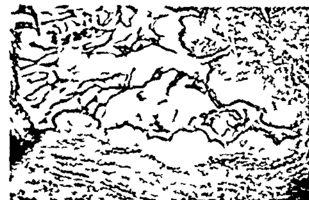


Fig 3 Fibrocellular papillary folds projecting into cystic space Note the abundant mucous secretion Stroma adjacent to the epithelium is composed of loosely arranged small fibroblasts continuing closely arranged forming a dense stroma Hematoxylin and eosin ×80



Fig 5 Areas in which the stroma shows [illegible] fibroblasts packed closely together [illegible] eosin ×200
(Inset) Higher magnification Note the large [illegible] hyperchromatic nuclei of the stromal cells Hematoxylin and eosin ×360

DISCUSSION

(1) described three polypoid lesions of endocer ... ngin which differed microscopically from the endocervical mucosal polyp and its variants He ...red them to be true neoplasms and termed papillary adenofibroma These tumors bore a resemblance to the adenofibroma of ovary ...ian tube and breast Vellios *et al* (8) described ...s of papillary adenofibroma 4 of them arising the endometrium In their opinion this tumor ... benign count rpart of the malignant mixed ...ermal tumor of the uterus of Müllerian origin ...malt et al (3) described the electron microscop... well as the histochemical characteristics of a ...f papillary adenofibroma of the endometrium ...roma of this tumor consisted exclusively of fi...sts associated with active fibrillogene is The ...ng epithelium of the papillary cystadenofibro...as of the mucinous secretory type and showed substructural similarities to the normal endo...al (2) and Bartholin gland epithelium (5) Fur...onfirmation of its close r semblance to endocer epithelium was provided by the histochemical ...s which revealed the p esence of abundant o- and carboxyacid mucins in the epithelium its secretions Similar findings were reported the normal cervical epithelium (6) Endometrial ...lium (1) and foci of squamous epithelium (8) found also as a covering epithelium of some ...e papillary cystadenofibromas The mucus ...ing epithelium is the result of metaplasia to ...ervical epithelium Similar metaplastic pro... occur in other endometrial lesions including ...e segment polyps and primary endometrial ...carcinoma (6) The multipotential nature of the ...al lining the Müllerian duct system explains metaplastic transformation of endometrial ...lium into endocervical tubal or squamous ...lium In our case all the lining epithelium prov... be of the mucus *secreting type* A direct ...logical continuity between the polypoid neo...a and the underlying endo- and myometrium was ...ned and in these areas a few glands and cysts ...ured by endometrial epithelium This supports ...eory that the mucus secreting epithelium of the ...and glands is the result of metaplasia

...e predominant fibroblastic growth and intricate ...tural organization of papillary cystadenofibro... ...uggests a neoplastic rather than a hyperplastic ...thelial endometrial stromal cell proliferation ...ese circumstances the covering epithelium appears to be a passive component If this is the real explanation then cystadenofibroma of the uterus is not the benign counterpart of malignant mesodermal tumor (8) where both components (mesenchymal and epithelial) are regarded as actively growing neo plastic elements

The detection and recognition of papillary cystade nofibroma of the endometrium is important mainly for the interpretation of material obtained by uterine curettage biopsies Confusion may arise between this lesion and that of endometrial stromatosis Both oc cur in pre and post menopausal women presenting with uterine bleeding In several cases endometrial stromatosis was described macroscopically as a poly poid mass protruding into and filling the endometrial cavity Microscopically the tumor consists of well dif ferentiated proliferating fibroblasts However en dometrial stromatosis is devoid of epithelial elements which seem to be the only reliable criterion for dif ferentiation between these two lesions Nevertheless there are cases where endometrial glands may be sur rounded and compressed by neoplastic stromal cells (4) The absence of mitoses is not a reliable criterion since endometrial stromatosis may also lack mitotic figures and the differential diagnosis then becomes more difficult when the fibroblastic growth in papillary cystadenofibroma displays nuclear atypia as illustrated in our case

All the reported cases of uterine papillary cystade nofibroma were of benign character both histologi cally and clinically Consequently the recognition and diagnosis of such lesions can be crucial in deciding the proper way to treat such patients and in predicting their prognosis

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CASE REPORT

HORMONE TREATMENT OF STROMAL ENDOMETRIOSIS

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bstract A report of two cases of recurrent stromal en metriosis both the patients having positive estrogen ceptors in the tumor tissue They were first treated with moxifen which failed to halt growth of the tumor After a onth s subsequent treatment with progesterone the tumor gressed and the patients condition improved

ndometrial stromal tumors are rare and constitute ly 0 2 per cent of all uterine malignancies (3 4) tho-anatomically the tumors develop from the oma cells of the endometrium without associated dometrial glands The clinical symptoms of these mors are somewhat variable but are generally un aracteristic the most frequent symptom being -rorrhagia An ambiguous nomenclature has led to ch confusion Among synonyms and related terms n be mentioned stromatosis endolymphatic stro-al myosis stromatous endometriosis and endome um interstitiale (7) Stromal endometriosis is often agnosed as a low grade sarcoma with a smooth ansition to real sarcomas The literature concerning omal endometriosis is scanty and we have found ly very few descriptions of the effect of pro-sterone on the tumor Two cases of stromal en metriosis treated by progesterone are presented d discussed

Case 1 A 27 year old patient was admitted to the necological department of the local hospital Previously had been essentially healthy Menarche had occurred at age of 13 and after that *menstruation* was normal 6/26 the age of 26 she had a normal partus (1963) In ptember 1964 she was subjected to curettage because of trorrhagia of one month s duration. Histology showed a perplastic corpus endometrium As the metrorrhagia con ued and it was thought to be caused by fibromyomas a tal hysterectomy was carried out Histology showed omal endometriosis with a homogeneous benign impres n, but with local invasive growth into the serosa in a few places It was limited to the corpus of the uterus and during the operation no signs of spread to the abdomen were found The patient remained well until November 1975 when she developed a colovaginal fistula A resection of the colon sigmoideum and closing of the fistula was carried out A radical operation was not possible owing to the presence of tumor masses in the small pelvis Histology showed stromal endometriosis with dedifferentiation more pro-nounced relative to that in earlier biopsies and tumor in the colon and vagina No postoperative problems arose and the fistula remained closed From April 6 1975 to January 13 1977 the patient was treated with estradiol tablets 2 mg (Progynon[R]) 1 tablet daily because of climacteric symp-toms On examination in January 1977 a relapse was observed and the patient was referred to the Radiumsta tionen Finseninstitutet Copenhagen On January 14 1977 a polypoid tumor measuring 3×2 cm was found in the top of the vagina which was fastened to the left side of the pelvic wall by a tumor mass the size of a mandarin orange Histology showed stromal endometriosis In addition estrogen receptor concentration was estimated It was $4\ 7 \times 10^{-14}$ mol/mg protein i e positive (lower limit ? $\times 10^{-14}$ mol/mg protein) Progesterone receptor was not estimated An i v pyelogram which earlier had been normal now showed hydronephrosis on the left side From January 14 to February 8 1977 the patient was treated with tablets hydrocortison 20 mg (Hydrocortison[R]) 1 tablet $\times$ 3 During this period gynecological examinations showed no change Because of the positive estrogen receptor result the patient was treated with tablets tamoxifen 10 mg *(Nolvadex[R]) 1 tablet × 3 from February 8 to March 8* 1977 In this period the patient s condition deteriorated with vaginal bleeding abdominal pains and progression of the tumor Since the tumor now measured 4×3 cm and the infiltration in the small pelvis had spread to the posterior wall treatment with tablets medroxiprogesterone acetas 100 mg (Clinovir[R]) 1 tablet daily was started on March 22 1977 and still continues The patient s condition improved drastically after this change of treatment and the abdominal pain and vaginal bleeding ceased within *14 days The patient* has been examined regularly since and the size of the tumor has diminished steadily By October 26 1977 there was no sign of tumor in the vagina and no tumor masses were palpable in the small pelvis An i v pyelogram on December 14 1977 was normal Roentgen examinations of the chest have always been normal At the last gynecological ex amination there was no sign of tumor and the patient felt well



Fig 1 Patient 1 Compact masses of spindle shaped cells permeate the myometrium along or within the lymphatics veins or tissue spaces and herniate into the vessels (Original magnification × 25)

Patient 2 The patient 45 years old was admitted to the gynecological department of the local hospital Formerly she had been essentially healthy The menarche had occur red when the patient was 14 since then menstruation had been regular The patient had never been pregnant In 1970 she had metrorrhagia and due to suspicion of fibromyomas a total hysterectomy was carried out Histology showed stromal endometriosis without signs of invasive growth There were however islands of stromal tissue in relation to veins and lymphatics At operation there was no sign of spread to the abdomen Because of climacteric symptoms the patient was treated with injections of estradiol benzoate 10 mg (Follicyclin[R]) every 2 – 3 months from 1974 to April 1976 In March 1976 the patient had abdominal pain and yellow brown fluor vaginalis and on gynecologic examina tion a 1 × 3 cm polypoid tumor was found in the top of the vagina connected to a mass in the small pelvis At ex plorative laparotomy a 3 × 3 cm metastasis on the peritone um was found besides tumor tissue in the pouch of Douglas and on the intestines Biopsy showed stromal endometriosis as previously On July 22 1976 the patient was examined at the Radiumstationen Finseninstitutet for the first time as she still had abdominal pain On gynecologic examination a 3 × 1½ cm vaginal tumor was found which was fixed to the right wall of the pelvis by a smaller mass Biopsy showed stromal endometriosis Estrogen receptor estimation was positive — 4.2×10^{-14} mol/mg protein Progesterone receptor estimation was negative The first treatment was i v injections of Rubidaxon 200 mg from July 28 to December 1 1976 During this period the tumor remained stationary but the patient still had pain The treatment was stopped because of ECG changes Due to the positive estrogen receptor result treatment with tablets tamoxifen 10 mg (Nolvadex[R]) 1 tablet × 3 was given from February 1 to March 2 1977 This resulted in significant deterioration of the patient s symptoms with vaginal bleeding increased ab dominal pain and progression of the tumor which now measured 3 × 3 × 2 cm and was fixed to the pelvic wall on both sides On March 24 1977 treatment with tablets medroxiprogesterone acetas 100 mg (Clinovir[R]) 1 tablet daily was started Within the first mon h the [illegible] dition improved significantly the vaginal [illegible] abdominal pain ceased The pa ient was [illegible] and the size of the tumor was observed to decrease [illegible] At the last control on July 11 1978 the tumor [illegible] × 2 cm and nothing abnormal was found in the pelvis The patient remains in good con[illegible] ment continues Roentgen exam[illegible] of the [illegible] all the time been normal I v pyelogram has not been [illegible]ried out

DISCUSSION

The long symptom free periods in the two [illegible] respectively 11 and 6 years before relapse [illegible] characteristic This is in accordance w[illegible] report (1) in which relapse occurred up to [illegible] after the diagnosis of stromal endometriosis [illegible] made Both our patients were under estrogen [illegible] ment for 1 and 2 years respectively before [illegible] appeared The role this treatment plays in [illegible] or accelerating the growth of recurrence is [illegible] but an earlier report has shown that the growth [illegible] this kind of tumor may be stimulated by e[illegible] Successful treatment of stromal endometri[illegible] progesterone was first described in 1968 by P[illegible] when a patient with lung metastases rem[illegible] symptoms after 7 years of treatment and was [illegible] sidered completely cured In the literature [illegible] been able to find 3 additional cases of stromal [illegible] dometriosis treated with progesterone A [illegible] response was mentioned in all the cases [illegible] complete disappearence of the tumor In our [illegible] tients the tumor disappeared completely in one [illegible] and diminished drastically in the other [illegible] ports the general impression that proges[illegible]

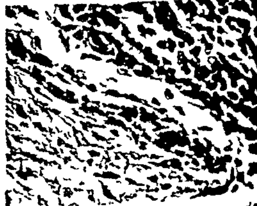


Fig 2 Patient 2 Spindle-shaped cells [illegible] dometrial stroma and have a large round or [illegible] Musculatur lower left field (Original magnification [illegible])

ory effect on endometrial stromal tumors estimations on this type of tumor not been performed before and the positive suggest that the antiestrogen therapy with was effective On the other hand the s treatment with antiestrogen had failed to the growth of the tumor or the deterioration of ts symptoms

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1982

Date	Place	Name	Office
1980			
October 3 – 5	New Delhi India	3rd International Seminar on Maternal and Perinatal Mortality Pregnancy Termination and Sterilization	Hon General Secretary The Fed [illegible] Obstetric & Gynecological Societies [illegible] India Purandare Grua 31 [illegible] Dr N A Purandare Marg Bombay 400 00[illegible] India
Oct Nov 23 – 3	San Marino Italy	The Gonadotropins Basic Science and Clinical Aspects in Females	Leslie Nies Symposia Manager Sero Symposia 11 Brooks Drive, Braintree MA 02184 USA
November 14 – 17	Madrid Spain	7 Congrès Européen de Medecine Perinatale	Professor de la Fuente Maternidad de la Ciudad Av Generalissimo 177 Madrid 16, Sp[illegible]
November 18 – 23	New Orleans LA USA	AAGL Ninth Annual Meeting Clinical Symposium on gynecologic endoscopy	American Association of Gynecologic Laparoscopists 11239 South Lakewood Boulevard Downey California 9[illegible]
November 20 – 22	Barcelona Spain	Symposium International Sobre Monitarizacion Prenatal	Instito Dexeus Srtas M Luz Cas[illegible] Ana Baldrich c/Paseo de la Bonanova 67 Barcelona 17 Spain
November 22 – 25	Bombay India	First National Congress on Hormones and Human Reproduction	Mahendra N Parikh Organizing Secretary Dr Jhaveri's Hospital [illegible] Lady Hardinge Road Bombay 4[illegible] India
December 1 – 4	Kairo Egypt	Second Congress of the International Society for the Study of Hypertension in Pregnancy	Docent Hjördis Robbe Dept of Obstet and Gynecol Karolinska Hospital S-104 01 Stockholm 60 Sweden
December 1 – 12	Melbourne Australia	Seventh UICC Training Course in Cancer Research	Dr A W Burgess UICC Course The Walter and Eliza Hall Institute Royal Melbourne Hosp P O 3[illegible] Victoria Australia

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CASF REPORT

ENDOMETRIOID CARCINOMA IN AN OPERATION SCAR

Hans Madsen Peer Hansen and Ole Peter Andersen

From the Department of Obstetrics and Gynecology Aalborg Hospital Denmark

ract A case of primary endometrioid carcinoma in en -triosis in an operation scar is described

ometriosis is a common disorder most frequently -ted in the ovaries uterosacral ligaments and oneum Endometriosis is seldom found in an -ation scar (3)

evelopment of carcinoma in endometriosis is ex nely rare Endometrioid carcinoma most com nly occurs in the ovary (2) extraovarian lesions ng only been observed in very few cases and then nly in the rectovaginal septum (2) however a le case of endometrioid carcinoma in the pleura been described (1) Endometrioid carcinoma loping within endometriosis in an operation scar not previously been reported

CASE REPORT

-year-old woman was admitted with a history of ab inal tumor She also complained of increasing ab inal pain extending over six months and a swollen ab en She had had six normal deliveries and 17 years pre ly had an abortion by means of a hysterotomy combin ith sterilization No gynecological symptoms were ed except for menopausal hot flushes during the pre ng year Her menstrual cycle was regular apart from months amenorrhea six months ago and she was re ng no hormonal therapy Since her operation 17 years slight pain in the scar at the time of menstruation had n noted

bdominal examination revealed a tumor of 12 × 12 cm he operation scar Pelvic examination was normal A sy from the tumor revealed carcinoma on histological on presumably a metastasis from ovarian car Tumor located in the left rectus abdominis was removed from the abdominal wall The tumor containing a dark brown fluid Apparently the was radically removed Both ovaries appeared to be normal with no sign of endometriosis light microscopic examination concluded mucin uterine carcinoma developing in endometriosis l wall as the connective tissue contained cysts with an endometrioid appearance and exhibited an in terval phase which corresponded with the patient s menstrual cycle The same histological characteristics were observed by electron microscopic examination

Roentgen ray examination of the colon was normal Fractional uterine curettage disclosed by histological ex amination endometrium in the secretory phase without pre malignant alterations

Postoperatively the patient was treated by radiotherapy in a dose of 5 500 rads in the abdominal field and 1 600 rads in the pelvic field Castration was additionally performed The patient was in perfect health at the conclusion of treat ment

DISCUSSION

Based on clinical tests operative findings and histolo- gy this case undoubtedly represents a primary endo metrioid carcinoma developing in endometriosis of an operation scar

There are two main theories about the genesis of endometriosis

1 The metastasis theory proposes that the en dometriotic tissue in some way is transported to an extrauterine location

2 The metaplasia theory suggests that the en dometriotic tissue arises by metaplasia of the cells in some extrauterine location

Steck & Helwig (3) describe a combination of these two theories in that endometrial cells themselves stimulate imitative metaplasia when they are trans ported by any means to a susceptible tissue

Due to the implantation of endometrial tissue in the scar at the time of operation the origin of the en dometriosis in the present case appears to be in accor dance with the metastatic theory

The reason for the development of carcinoma in endometriosis is unknown but it seems quite pro- bable that important factors concerned with the de velopment of carcinoma in the endometrium of the corpus uteri also are important for development of endometriod carcinoma

ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1982

Date	Place	Name	Office
1981			
January 26 – 31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Cong [illegible] 31600 West Chicago [illegible] USA
March 14 – 18	Atlanta USA	37th Annual Meeting of the American Fertility Society	The American Fertility Society 1608 13th Avenue So[illegible] Birmingham Alabama 352[illegible] USA
March 22 – 26	Berlin West-Germany	IIIrd World Congress of Human Reproduction	Dozent L. Mettler Frauenk[illegible] Hegewischstr 4 D-2300 Kiel 1
March 27 – 28	Modena Italy	Symposium on Recent Advances on Patho-physiology of Amniotic Fluid	Scientific Secretariat Dr G C D[illegible] Istituto di Clinica Os[illegible] e Gine cologi a Policlinico Via del P[illegible] 41100 Modena Italy
April 15 – 17	Gorizia Italy	International Course on Ultrasound in Obstetrics	Filippo Destro Organizing Secr[illegible] Dept of Obstetrics and Gynecolog[illegible] City Hospital Via [illegible] 34170 Gorizia Italy
May 17 – 24	Dubrovnik Yugoslavia	4th European Congress on Ultrasonics in Medicine	Professor Asim Kurjak [illegible] Stube 41000 Zagreb Yugoslavia
June 9 – 12	Ostend Belgium	Third International Congress on the Menopause	The International Menopause Soc[illegible] 8 av Don Bosco 1150 Brussels [illegible]
July 1 – 4	Graz Austria	First International Symposium on Minimal Invasive Cancer (Microcarcinoma)	Secretariat First Sympos[illegible] on Minimal Invasive Cancer P O B[illegible] A – 1014 Wien Austria
August 24 – 28	Cambridge England	XIII Acta Endocrinologica Congress	Conference Services Ltd XIII Acta Endocrinologica Congress [illegible] London SW7 3[illegible] England
Sept-Oct	Athens Greece	VIth European Congress on Sterility (ESCO)	Sekretariat Prof Dr K Se[illegible] Klinik der Univers[illegible] Kiel, Heg[illegible] strasse 4 2300 Kiel 1 West Germ[illegible]
October 25 – 31	Melbourne Australia	Eight Asian Congress of Obstetrics and Gynecology	The Organizing Secretary VI[illegible] Congress of Obstetrics and Gy[illegible] G P O Box [illegible]195T Melbourne [illegible] Victoria Australia
1982			
October 17 – 22	San Fransisco CA USA	Xth World Congress of Gynecology and Obstetrics	Xth World Congress of Gynecology [illegible] Obstetrics c/o The American C[illegible] Obstetricia[illegible] and Gynecolog[illegible] One East Wacker Dr[illegible] Chicago Illinois 60601 USA

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ANTENATAL CARDIOTOCOGRAPHY AND INTRAUTERINE DEATH

Thore Solum and Nils Otto Sjöberg

From the Department of Obstetrics and Gynecology University of Lund Lund Sweden

...act The purpose of the present study was to elucidate ...e reliability of antenatal cardiotocography (CTG) in ...ed...ing fetal death During a 4-year period 1455 patients with risk pregnancies have been routinely monitored with ...l CTG The total number of tracings amounted to ... than 10000 Five cases of fetal death occurred in all ...hich pathological CTG patterns were found Our expe...ence in the present study indicates that antenatal CTG is a ...liable technique for the predicting of fetal death and its ...se should reduce fetal mortality rates

...ardiotocography (CTG) was introduced in the six... after fundamental studies by Caldeyro Barcia ...ammacher and Hon (2 10 12) Although interest ...ocused mainly on intrapartal CTG monitoring ante...atal monitoring soon attracted attention too (13) The interpretation and value of antenatal CTG how... has been a matter of dispute and Beard (1) ...ated in 1974 that experience of antenatal CTG was ...o limited to allow of an evaluation of its reliability ...uring recent years more experience has accumulated ...y reports have been published on the subject ...e interpretation of CTG intrapartally as proposed ... Hammacher and Hon (10 12) seems to be general... accepted In antepartal monitoring their interpreta...on has also been of fundamental importance On ...s basis various scoring systems have been develop... (4 9 14 17 19 24) However in some studies so-...led fetal heart reactivity has received most at...tion in the assessment of fetal condition (4 6 16 ... 20)

Whatever classification of the various CTG pat...rns might be chosen the main question must be ...ether antenatal CTG can be used as a reliable ...reening test for identifying the fetus at risk In this ...spect one would be prepared to accept some cases ...f false pathologic tracings (over diagnosis) The oc...currence of false normal tracings however is not ...hat one would expect from a reliable screening test

One essential aim of all antenatal care is to prevent fetal death and the purpose of the present work was to elucidate the reliability of antenatal CTG in predicting fetal death

MATERIAL AND METHODS

In the catchment area of the Department of Obstetrics and Gynecology of the University Hospital in Lund practically all pregnant women visit the antenatal clinics regularly during pregnancy For various complications about 15 per cent of them are hospitalized for shorter or longer periods during the last part of the pregnancy From March 1976 to March 1980 1899 patients were hospitalized on the antenatal ward Apart from some exceptions during the first months of the period studied all patients which at least had reached the 28th week of gestation were monitored daily with CTG Thus 1455 patients (76 6 per cent) have been routinely monitored with CTG The mean number of diagrams per patient was 7–8 and the whole material therefore consists of more than 10000 cardiotocograms In the whole material ultrasound fetal cardiography was generally used Only in selected cases was abdominal fetal electrocardiography performed In all 5 cases reported ultrasound fetal cardiography was used Each CTG has been sorted according to the classification shown in Table 1 Only one criterion

Table I Classification of antenatal CTG

Class 1 (Normal CTG)
Baseline 120–160 beats/min
Variability (band width) > 10 beats
No decelerations

Class 2 (Suspect pathological CTG)
Baseline 100–120 or 160–180 beats/min
Variability (band width) >25 beats
Variability (band width) 5–10 beats for less than 10 min
No accelerations

Class 3 (Slight pathological CTG)
Baseline <100 or >180 beats/min
Variability (band width) 5–10 beats for more than 10 min
Scattered moderate variable decelerations

Class 4 (Severe pathological CTG)
Variability (band width) <5 beats
Severe variable decelerations
Late decelerations

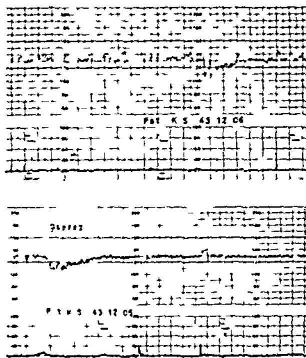


Fig 1 Antenatal CTG from case 1 demonstrating severe pathological changes Upper and lower tracings show parts from the same recording The frequency is about 130 beats per minute (bpm) The variability in the upper tracing seems normal but in the lower part the variability is clearly decreased The externally registered tocogram does not reflect the uterine contractions very well but after two contractions late decelerations are induced

was needed to refer the patient to one of the classes During the first 2 years of the period the traces were judged by the authors However as the classification proved to be convenient and reliable (2) interpretation of the antenatal CTGs has since been performed by several members of the staff

RESULTS

Of the 1455 patients routinely monitored with CTG during the 4 year period 5 cases of fetal death occurred (0 34 per cent) In each of these 5 cases pathological CTG patterns were seen on the traces

Case 1 A 33 year-old woman gravida 3 para 2 was admitted in July 1976 in the 33rd week of gestation by reason of pre-eclampsia and intrauterine growth retardation (IUGR) CTG was performed 2–3 times per week Sixteen days after admission the CTG showed severe pathological changes (Class 4) (Fig 1) This CTG abnormality was overlooked and therefore no further CTG was done during the subsequent

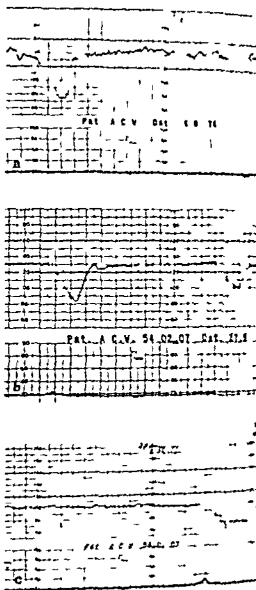


Fig 2 Antenatal CTG from case 2.
a) CTG trace on admission The frequency is [illegible] bpm The variability shows silent pattern [illegible] contractions profound decelerations are present
b) CTG tracing one day after admission The [illegible] about 130 bpm the variability shows [illegible] decelerations occur one after [illegible]
c) CTG tracing [illegible] days after admission [illegible] tern the frequency is about 100 bpm [illegible]

days Four days after the last CTG fetal [illegible] death was diagnosed

Case 2 A 22 year-old woman gravida 2 [illegible] admitted in the 31st week of gestation by reason [illegible] pre-eclampsia and IUGR The size of the [illegible]

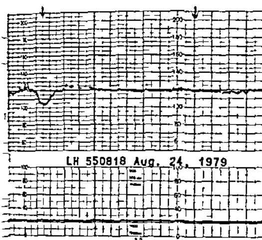


Fig 3 Antenatal CTG from case 3 The frequency is about 120 bpm Silent pattern and deceleration are present the day before fetal death No contractions were visualized on the tocogram.

responded to the 27th week of gestation and the fetus was not judged viable *ex utero* Already on admission there pathological CTG patterns occurred (Fig 2 a) During the next 2 days an aggravation of the ominous pattern took place and the fetus died *in utero* (Figs 2 b c)

Case 3 A 24-year-old primigravida was admitted in the 29th week of gestation by reason of pre eclampsia and IUGR The size of the uterus corresponded to the 25th week of gestation The fetus was not judged viable *ex utero* On the day after admission a severe pathological CTG pattern was seen (Fig 3) Two days after admission no fetal heart sounds could be detected

Case 4 A 42 year-old woman gravida 2 para 3 was admitted in the 29th week of gestation by reason of pre-eclampsia A twin pregnancy had earlier been diagnosed and the fetuses had been thoroughly examined by ultrasound scanning IUGR had been diagnosed in one of the twins CTG was normal on both twins during the first days (Fig 4 a) After 8 days the IUGR twin showed a slight pathological CTG (Fig 4 b) During the subsequent days the CTG patterns worsened (Figs 4 c d) Fourteen days after admission the IUGR twin showed no signs of life Throughout the period the other twin showed a normal CTG and both the dead and the living twin were delivered in the 39th week of pregnancy

Case 5 A 37 year old woman gravida 4 para 2 was admitted in the 33rd week of gestation by reason of pre-eclampsia and IUGR After a day the first slight pathological CTG occurred (Fig 5 a) After 2 days the pattern worsened (Fig 5 b) and an oxytocin stress test (OST) was performed which proved clearly positive (Fig 5 c) It was decided to administer cortisone for lung maturation and the next day the CTG was normal (Fig 5 d) On the fifth day repeated ominous CTGs occurred (Fig 5 e) Cesarean section was decided on later the same day but the child was stillborn

DISCUSSION

Various methods exist for the supervision of mother and fetus during pregnancy For instance blood pressure and symphysis fundal measurements are used routinely in all pregnancies to estimate the progress of pregnancy Despite this the existing methods have been considered inadequate and consequently search has been made for a reliable method that could be used in all pregnancies for detection of the fetus at risk A perfect screening method in this respect must be convenient for both the patient and the personnel It should be neither too expensive nor too time-consuming The results must always be unequivocal easy to interpret and no false normal results should occur Does antenatal CTG fulfil these criteria? The answer is no because CTG is time-consuming and places considerable demands on the staff and is therefore expensive For personnel who are not specially trained it can be difficult to arrive at a correct interpretation In order to discover the risk cases during pregnancy continued use of the routine methods combined with ultrasound scanning is preferable at the antenatal clinics

In our catchment area about 15 per cent of all pregnant women have been hospitalized because of pathologic findings at routine examination (including ultrasound scanning) at the antenatal clinics or because of acute incidents such as bleeding and premature contractions In a previous report we stated that about 40 per cent of these patients could be classified as high risk patients (22) Nearly all the pathologic antenatal CTGs were found in this group The conclusion was therefore that primarily high risk patients should be routinely monitored with antenatal CTG In the present study this conclusion was confirmed by the fact that all cases of intrauterine death had the diagnosis pre eclampsia and IUGR

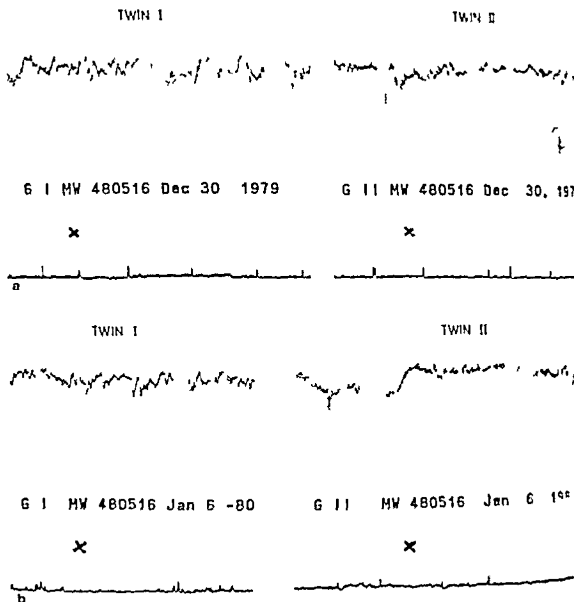


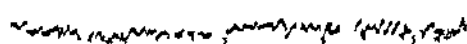
Fig 4 Antenatal CTG from case 4
a) One day after admission both twin I and twin II show normal CTGs

b) Nine days after admission Twin I shows [illegible] The CTG from twin II demonstrates a [illegible] bpm and one deceleration of variable appearance

As intrauterine death so seldom occurs it is necessary to study a large number of patients in order to evaluate the reliability of CTG monitoring in predicting these cases In the present investigation more than 1400 patients and 10000 CTGs were studied Five intrauterine deaths occurred during the observation period In each of these cases pathologic changes in the CTG pattern predicted the outcome

Since the early description by Hon of changes in fetal heart rate preceding fetal death (11) many reports have been published on the subject [illegible] Kubli *et al* (15) reviewed 13 cases of [illegible] death In all but one case pathologic CTGs [illegible] same nature as in the present report were fo[illegible] unpredicted case had no antepartum CTG [illegible] 48 hours prior to intrauterine death In other [illegible] the reliability of CTG in predicting fetal dea[illegible] also been stressed (3 7 8 23)

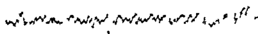
Although fetal death can occur [illegible] changes this seems to be extremely rare [illegible]



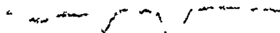


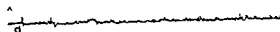












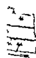
…n days after admission Twin I shows normal CTG …CTG from twin II demonstrates silent pattern and …lerations of sinusoid appearance

d) Thirteen days after admission (less than 24 hours before fetal death) Twin I shows normal CTG The CTG from twin II shows silent pattern and decelerations

…mong our own patients and also in the case reported …Kubli (15) the explanation could be too long an interval between registrations It would therefore seem …tified to conclude that the intervals should not exceed 2 days In cases of umbilical cord complications …which may occur antenatally and *ablatio placentae* the ability of CTG to predict fetal death might not be sufficiently reliable However van Wering *et al* (25) published 4 cases of *ablatio placentae* where CTG warned of fetal distress

As mentioned in the introduction one would be prepared to accept some cases of false pathologic











…5 Antenatal CTG from case 5
…ne day after admission The frequency is 125 – 130 …, decreased variability and one deceleration

b) Three days after admission Repeated decelerations of uncertain nature (no contraction visible)

c) Oxytocin stress test 3 days after admission Decreased variability and repeated late decelerations after each con traction

d) Four days after admission and af er cortisone adm... tion Normal CTG is registered

CTG (over diagnosis) provided all fetuses at risk could be identified In the present study 5 cases of in trauterine death among 1455 CTG monitored pa tients were retrospectively examined concerning the CTG patterns preceding fetal death In all 5 cases se vere pathological CTG patterns were found During the investigated period approximately 50–60 more patients (4 per cent) showed severe pathological CTG patterns (22) These patients were all delivered within a few hours after the appearance of such patterns The proportion of over diagnosis among these cases cannot be evaluated The results of the present study together with reports from other authors support the view that prompt action must be taken to deliver a fetus showing severe pathological CTG patterns Although the proportion of overdiagnosis cannot be enumerated exactly CTG must be considered a most reliable method of predicting fetal death

e) Five days after admission (same day as fetal death occur red) Decreased variability and one deceleration probably of late na ure

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MATERNAL FETAL AND NEONATAL EFFECTS OF BETA ADRENERGIC STIMULATION IN CONNECTION WITH CESAREAN SECTION

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stract To investigate the combined metabolic effects of ta-mimetic therapy and general anesthesia on maternal d fetal/neonatal metabolism 14 patients were treated th isotonic saline 11 with intravenous fenoterol (3 µg/ n) and 9 with intravenous isoxsuprine (150 µg/min) for 30 nutes prior to cesarean section The maternal heart rate d blood pressure as well as the maternal and fetal acid se balance were followed The neonatal glucose level was nitored for 36 hours after delivery

The heart rate and the diastolic and systolic blood pres re values increased during the operation in each group thout any marked differences between the groups At livery the mean maternal BD (base deficit) value was her in the fenoterol patients than in the control patients licating a trend towards metabolic acidosis The other lues of acid base balance in the maternal and umbilical erial and venous blood did not reveal any differences be The neonatal glucose level at 2 hours after as higher in the fenoterol group than in the con l group The other values recorded during 36 hours re led no differences between the groups

Beta mimetic treatment preceding general anesthesia in sarean section does not have unfavorable effects on the ther the fetus or the newborn Such therapy thus does t seem contraindicated when uterine contractions should rapidly suppressed in cases of fetal distress before opera n.

Beta-sympathomimetic drugs have been used increas ingly in obstetric practice to suppress uterine contrac tions (8 16 17) It has also been shown that fetal stress and acidosis can be successfully treated with tocolytics (3 7 10) possibly by improving utero-placental circulation (17)

Cesarean section involves stress factors which may those of vaginal delivery deteriorate the placental circulation and affect the fetus and the newborn infant as shown by the Apgar scores the acid-base values and the neonatal morbidity and mortality (2 15) The condition of the newborn in fants after cesarean section correlates possibly best to the placental perfusion during the anesthesia induc tion — delivery interval (9 12) It would thus be ideal to maintain the placental blood flow as well as pos sible during this time The beta sympathomimetic drugs could theoretically be of value in this respect

The purpose of this study was to elucidate the ef fects of preoperative intravenous infusion of feno terol and isoxsuprine on maternal fetal and neonatal metabolism and maternal circulation in connection with elective cesarean section performed under general anesthesia in normal pregnancies

MATERIAL AND METHODS

The series consisted of 34 healthy mothers in the 38th—43rd week of normal pregnancy (Table I) The indication for elective cesarean section was a feto-pelvic disproportion in 29 cases and previous cesarean sections in 5 cases None of the mothers had uterine contractions prior to the study The study and its purpose were explained to the mothers and their consent was obtained

At 8 00 a m an i v infusion of isotonic saline (14 cases control group) fenoterol (11 cases) or isoxsuprine (9 cases) was started and maintained for 30 minutes The infusion rate for fenoterol was 3 µg/min and that for isoxsuprine 150 µg/min General anesthesia was induced 10 minutes after the cessation of infusion

Table I *Age parity and gestational weeks of the parturients examined*

Group		Age	Parity	Gestational weeks
Control group	mean	29 0	2 0	40 2
(n = 14)	range	19 – 38	1 – 3	39 – 43
Fenoterol group	mean	27 3	1 9	39 9
(n = 11)	range	18 – 43	1 – 5	38 – 42
Isoxsuprine group	mean	26 1	1 8	40 0
(n = 9)	range	19 – 30	1 – 3	39 – 41

Table II *The mean (±SD) induction doses of thiopental induction–delivery interval (I–D time) and blood losses during cesarean section*

Group	Doses of thiopentone total (mg)	Doses of thiopentone mg/kg	I–D time	Blod loss (ml)
Control group	277	4 2	8 35	981
(n=14)	±31	±0 8	±2 30	±361
Fenoterol group	300	4 4	7 49	894
(n=11)	±35	±0 4	±2 17	±217
Isoxsuprine	278	4 1	7 40	789
group (n=9)	±51	±0 8	±1 13	±359

Table III *The weight and Apgar score of infants*

Group		Birthweight (g)	Apgar 1 min	Apgar [illegible]
Control group	mean	3 284	[illegible]	[illegible]
(n=14)	range	2 600–4 700	[illegible]	[illegible]
Fenoterol group	mean	3 339	[illegible]	[illegible]
(n=11)	range	2 810–4 000	[illegible]	[illegible]
Isoxsuprine group	*mean*	3 6 6	[illegible]	[illegible]
(n=9)	range	[illegible]860–4 640	[illegible]	[illegible]

Th[illegible] ati[illegible] n s were unpremedicated Before the induction 0 5 mg atropine i v was given Oxygen was administered by [illegible] 3 minutes after which thiopental for the induction [illegible] s a was given (Table II) and endotracheal intuba [illegible] a [illegible] mplished with the aid of succinylcholine (1 [illegible] sthesia was maintained with a mixture of [illegible] and [illegible] n 1 1 and succinylcholine infusion [illegible] on the operation table was at least 15 left [illegible] avoid aortocaval compression [illegible] and blood pressure were recorded every five m[illegible] the infusion and the operation at th[illegible] beginning [illegible] peration and at the moment of delivery [illegible] was continuously monitored Ma[illegible] nal [illegible] se balance and PO_2 were determin ed [illegible] tion of anesthesia and at the mo ment o[illegible] cal cord was double-clamped at th[illegible] and umbilical arterial and venous samp s were d aw [illegible] fo determination of the acid base balance [illegible] samples were taken anaerobically in to heparin[illegible] ed gla[illegible] s and analyzed immediately pH PCO_2 and PO_2 were determined with a Radiometer [illegible] analyzer Base deficit was calculated using Si[illegible] Andersen s nomogram Neonatal blood samples for [illegible] determination were taken at the ages of 2, 6, 12, [illegible] hours Glucose was assayed according to the g[illegible] oxidase method (Gemsaec block 1978) The sta[illegible] analyses were made using Student s t-test

RESULTS

The outcomes of the anesthesias and the cesarean sec tions were uneventful with the exception of [illegible] mother in the control group who had tra[illegible] systoles for a few minutes after the induction of [illegible] thesia They recovered spontaneously The I[illegible] tervals and the amounts of blood lost were of [illegible] order in the different groups (Table II)

Table IV *Maternal heart rate and blood pressure (mmHg) at different times means±SD*

Group	Before anesthesia	At the beginning of operation	At delivery
Control group			
heart rate	98±22	115±21†	116±15*
systolic pressure	132±12	137±21	15[illegible]±18 †
diastolic pressure	88±9	94±18	104±13 †
pulse pressure	43±8	43±21	45±11
Fenoterol group			
heart rate	108±15	126±26	1 6 ± 4†
systolic pressure	*136±10*	*148±11†*	*156±99*
diastolic pressure	85±7	95±10	99±10
pulse pressure	51±9	51±12	57±10
Isoxsuprine group			
heart rate	115±20	143 ±7†	129 ±15
systolic pressure	1[illegible]4±13	144±13	143±15
diastolic pressure	77 ±8	93±1[illegible] †	97±14
pulse pressure	51±1[illegible]	53±14	*44±11*

† = $p<0.05$ from the initial †† = $p<0.01$ from the initial
* = $p<0.05$ compared with the control group ** = $p<0.01$ compared with the control group

ble V Maternal arterial umbilical arterial and venous blood pH P_{CO_2} (kpc) P_{O_2} (kpc) and BD (mmol/l) ans±SD

...oup	Maternal arterial before anesthesia	Maternal arterial at delivery	Umbilical venous	Umbilical arterial
...ntrol				
pH	7 43±0 04	7 35±0 04	7 30±0 04	7 26±0 04
P_{CO_2}	3 4±0 6	4 6±0 4	5 8±0 5	6 4±0 6
BD	5 2±2 0	5 9±1 1	5 0±1 5	5 8±2 2
P_{O_2}	14 5±0 8	22 9±3 3	5 2±1 1	3 2±0 7
...oterol				
pH	7 37±0 03	7 33±0 04	7 30±0 03	7 26±0 04
P_{CO_2}	3 9±0 5	4 4±0 4	5 8±0 2	7 1±0 9
BD	6 9±0 8	7 5±1 5	5 2±2 0	4 4±2 3
P_{O_2}	14 7±2 4	23 6±5 6	5 1±1 6	2 6±0 5
...xsuprine				
pH	7 39±0 03	7 34±0 04	7 29±0 02	7 26±0 02
P_{CO_2}	3 8±0 1	4 4±0 3	5 9±0 2	6 5±0 2
BD	6 7±1.2	6 8±1 3	5 4±1 0	6 2±2 0
P_{O_2}	16 0±1 5	22 9±6 1	5 3±0 6	3 7±1 4

p<0 05 compared with the control group

The newborns were in good condition after deliv y The Apgar scores at 1 min and 5 min did not dif t between the groups (Table III) One baby in the oterol group received 6 points at 1 min but 9 ints at 5 min

...ternal heart rate and blood pressure The lowest an *heart rate* before the induction of anesthesia s seen in the control group (Table IV) It did not wever differ significantly from the corresponding lues in the other groups In all of the groups the an heart rate increased during the anesthesia and e operation In the isoxsuprine group the mean art rate at the beginning of the operation was sig ficantly higher than the initial value (p<0 01) or e corresponding value in the control group (p< 01) At the moment of delivery the mean heart rate lues in the fenoterol and the isoxsuprine groups re significantly higher than in the control par ients (p<0 05)

able VI Blood glucose (mmol/l) of newborn infants er cesarean section means±SD

...oup	2 hours	6 hours	12 hours	24 hours	36 hours
...ntrol	2 7 ±0 4	2 7 ±0 8	2 8 ±0 8	2 5 ±0 7	2 6 ±0 7
...oterol	3 3 ±0 3	2 7 ±0 4	2 9 ±0 4	3 0 ±0 7	3 3 ±0 1
...xsuprine	2 6 ±0 6	2 8 ±0 4	2 9 ±0 5	2 8 ±0 5	2 7 ±0 6

p<0 05 compared with the control group

Before the induction of anesthesia the lowest mean *systolic blood pressure* was recorded in the isox suprine group (Table IV) This value differed signifi cantly from that in the fenoterol group (p<0 05) At the other times there were no statistically significant inter group differences in the systolic blood pres sures In all the groups the mean systolic blood pres sure increased significantly during the anesthesia and the operation In the fenoterol and the isoxsuprine groups this increase was more rapid than in the con trol group

The lowest mean initial *diastolic pressure* was seen in the isoxsuprine group (Table IV) This value dif fered significantly from that in the control group (p<0 05) The mean diastolic pressure also increased during the operation The mean values recorded at delivery were significantly higher than the mean in itial values in all the groups (p<0 01)

The mean *pulse pressure* did not change signifi cantly during the opeartion in any group At delivery the mean pulse pressure in the isoxsuprine group was significantly lower than in the fenoterol group (p< 0 05)

Maternal and fetal acid base balance Before the in duction of anesthesia there were no significant inter group differences in the maternal arterial acid base values or PO_2 At the moment of delivery these val ues were at the same level as initially At that time however the mean maternal base-deficit (BD) in the fenoterol group was significantly higher than in the control group (p<0 05) (Table V)

The umbilical arterial and venous acid base values and PO_2 did not differ significantly between the groups (Table V)

Neonatal glucose At the age of 2 hours the mean neonatal glucose of the fenoterol group was significantly higher than that of the control group ($p<0.05$) (Table VI) At the other times there were no significant differences between the groups The decrease between 2 and 6 hours after delivery in the fenoterol group was significant ($p<0.05$) while at the other times the glucose values did not differ from the 2 hour level in any group

DISCUSSION

During the induction of general anesthesia for cesarean section the placental blood flow has been shown to decrease (12) In connection with an elective section in normal pregnancies however this seems to be of no great clinical importance The newborns are generally in good condition (9 12) The fetal distress caused by uterine contractions may, however be increased because of the anesthesia In such cases pretreatment with beta mimetics might therefore be beneficial and improve the fetal state However it is important to study first the effects of combined beta mimetics and anesthesia

The maternal cardiovascular effects of beta mimetic drugs are tachycardia and hypotension (20) Especially a fall in the diastolic blood pressure and a widening of the pulse pressure have been emphasized The cardiovascular and metabolic effects of the beta adrenergic drugs have been shown to become evident in a few minutes (6) The present findings concerning the maternal cardiovascular effects of fenoterol and isoxsuprine used in tocolytic concentrations are in accordance with the previous reports The lowest initial blood pressure and the highest pulse rate were observed in isoxsuprine parturients It is known that isoxsuprine in tocolytic concentrations has a more profound cardiovascular action than fenoterol (6) The patients in the fenoterol and isoxsuprine groups responded to the anesthesia and the operation more markedly than the controls This was evidenced as a greater rise of blood pressure in the beta mimetic patients The present healthy mothers had no controversial effects of this In patients with cardiovascular diseases however the beta mimetics should be avoided because of the risk of an incipient cardiac decompensation which has been shown to occur after high doses of beta mimetics (1)

The main maternal metabol[illegible] beginning of an infusion of beta [illegible] lipolysis and glycogenolysis [illegible] mediately (13 20) The changes in th[illegible] base balance which have been shown [illegible] acute metabolic acidosis are [illegible] primary changes In the present study the [illegible] acid base parameters also showed a [illegible] metabolic acidosis in the fenoterol [illegible] higher BD values than in the con[illegible] detected

An ideal placental blood flow is the [illegible] for fetal well being During the general [illegible] cesarean section there are factors which [illegible] placental perfusion (12) Beta stimula[illegible] vasodilatation together with a widened [illegible]tude and an increased cardiac output [illegible] enhance placental perfusion (?1) There a[illegible]tions which have shown beta m[illegible] able effects on intrapartum fetal acidos[illegible] ed fetal capillary blood PO_2 values have [illegible]ported during an infusion of fenoterol ([illegible]) present cases of normal pregnancy [illegible] of placental disturbances and in [illegible] without uterine contractions the beta [illegible] not seem to have any remarkable effect [illegible] or the newborn as evidenced in the acid base [illegible]eters or the Apgar scores In cases of an [illegible] and uterine contractions these findings cou[illegible]ferent

During beta mimetic tocolytic therapy [illegible]lysis also occurs in the fetus (10) Th[illegible] action appears immediately after start[illegible] nous application of sympathomimetics (1[illegible]) On the other hand the previous results have [illegible] blood glucose values of the fetus the newborn [illegible] the mother at birth correlate with each other ([illegible]) The lowest neonatal glucose levels have been [illegible]ed at the age of two hours (5 11) [illegible] fore the first neonatal blood glucose levels were [illegible]sayed at this time They showed no [illegible] state in any of the babies In the fenoterol gro[illegible] mean neonatal blood glucose at th[illegible] cantly higher than in the control babies [illegible] reflects the hyperglycemic action of the drug [illegible] finding does not support the [illegible] an acute tocolytic therapy th[illegible] are depleted and fetal hypogly[illegible] the newborn (?0) According to [illegible] sient short term tocolytic therapy does not [illegible] have any harmful effects on neonatal [illegible]olism

The findings of this study show that general anesthesia and beta mimetics in healthy parturients do not have unfavorable combined effects on the either the fetus or the newbron In complicated pregnancies fetal distress may be caused or at least exacerbated by uterine contractions which diminish utero-placental blood flow In such cases the delivery is often terminated with cesarean section The attempt to obtain an immediate uterine relaxation with intravenous infusion of a beta mimetic drug prior to the operation seems in the light of the present results to be in no way contraindicated

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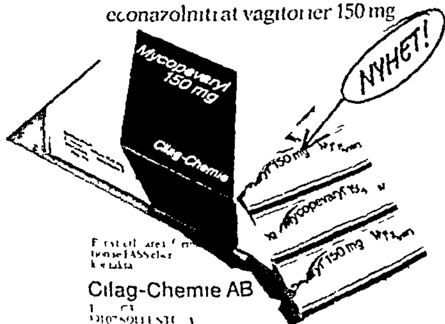


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MATERNAL ALCOHOL AND TOBACCO USE AND NAUSEA AND VOMITING DURING PREGNANCY

Relation to infant birthweight

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Abstract A recent report has documented a decreased probability of nausea and vomiting during pregnancy (NVP) in women who were *simultaneously* both regular drinkers and smokers, especially if these habits existed before pregnancy Maternal smoking and drinking have both been linked with decreased infant birthweight as has absence of NVP The question posed by these findings is whether the decrease in birthweight associated with absence of NVP is in fact due to use of maternal drinking and smoking The data presented in this paper indicate that this is not the case NVP is related to infant birthweight even after adjustment for maternal alcohol and tobacco use

The association of nausea and vomiting during pregnancy (NVP) with favorable pregnancy outcome has frequently been reported Risk of abortion prior to the 20th week of pregnancy is decreased if NVP is present (2 4 7 9) and live born children are reported to be of greater gestational age and higher birth weight (7)

However a recent report has linked probability of NVP with maternal alcohol and tobacco use (6) NVP was reported less frequently by women who were simultaneously both regular drinkers and smokers especially if these habits existed prior to pregnancy Maternal drinking and smoking have both been related to decreased infant birthweight (1 3 5 8) The purpose of this paper is to determine if presence of NVP is related to higher birthweight when maternal drinking and smoking habits and their relationship to NVP are taken into account

SUBJECTS AND METHODS

Subjects and methods in this investigation have been described in detail elsewhere (6) Briefly a consecutive sample of 806 prenatal patients in a large health maintenance organization were screened for alcohol and tobacco use The first 162 subjects plus all women drinking an average of at least 15 ml of absolute alcohol daily before pregnancy or in early pregnancy were studied (n = 222) Of these all women who bore single live children are included in this report (n = 199) An in-depth interview in the fourth month of pregnancy provided information on drinking since conception and in the 6 months prior to it as well as data regarding *smoking beverage consumption and drug use Alcohol* use was expressed in average milliliters of ethanol consumed daily (*AA Score*) *Regular* drinking was defined to be an AA score of 0 5 or more (equivalent to at least 30 ml of 100-proof whiskey daily) AA scores of 0 1 or less were classified as *infrequent* drinking with intermediate AA scores defined as *occasional* drinking *Smokers* lit an average of at least one cigarette per day Occurrence of NVP refers to nausea and vomiting in the first four months of pregnancy as reported by the subject

RESULTS

The initial analysis deals with drinking in the 6 months before pregnancy *Table I* shows mean infant birthweight by maternal smoking drinking and NVP status In general birthweight of infants was less if NVP was absent regardless of alcohol or tobacco use Other factors which might influence birthweight were then considered Table 2 shows mean maternal height age parity gestational age and per cent of male children in the groups Maternal age and sex of child were considered to be possible confounding variables These as well as AA score smoking and NVP status were regressed on birthweight Only AA score and NVP contributed significantly to the variance The equation was then recomputed with only *the three primary independent variables The result* is shown in Table 3 Addition of interaction terms failed to change the significance of NVP

The identical analysis was then repeated for early pregnancy drinking and smoking Again NVP was significantly related to infant birthweight even when

Table I *Mean birthweight of infants (gm) by maternal drinking smoking and NVP status (N = [illegible]*

	Occasional or infrequent drinking		Regular drinking	
	Nonsmoker	Smoker	Nonsmoker	Smoker
Before pregnancy				
NVP	3 622 (66)	3 521 (15)	3 583 (46)	3 4[illegible] (16)
No NVP	3 474 (20)	3 475 (7)	3 468 (11)	3 180 (15)
Early pregnancy				
NVP	3 631 (102)	3 437 (18)	3 459 (15)	3 359 (8)
No NVP	3 440 (29)	3 394 (14)	3 355 (4)	3 168 (9)

Number in subgroup shown in parentheses beside mean birthweight of subgroup

controlling for alcohol and tobacco use in early pregnancy Table I indicates that absence of NVP is linked to lower birthweight regardless of alcohol and tobacco use Regression of the three primary variables on birthweight (Table 3) confirms this observation Regression results are altered if number of cigarettes (rather than binary smoking status) is entered as the tobacco use variable during pregnancy then number of cigarettes contributes significantly to birthweight variance as does NVP

DISCUSSION AND SUMMARY

The hypothesis that the beneficial effect of NVP on birthweight is due to infrequent drinking and smoking among women with NVP is not supported by the data presented here In fact alcohol use (prior to pregnancy only) smoking (during pregnancy) and NVP each appear to be significantly correlated with infant birthweight According to these data, NVP may still be considered a favorable prognostic sign and not the reflection of abstaining from [illegible] tobacco and alcohol

ACKNOWLEDGEMENT

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Table II *Selected factors influencing birthweight by maternal drinking before pregnancy NVP and smoking status*

	Occasional or infrequent drinking		Regular drinking	
	Nonsmoker	Smoker	Nonsmoker	Smoker
Maternal height (cm)				
NVP	163	165	165	165
No NVP	163	165	165	165
Maternal age (years)				
NVP	26	26	29	[illegible]
No NVP	27	21	25	[illegible]7
Parity				
NVP	1	1	1	1
No NVP	1	1	1	1
Gestational age (weeks)				
NVP	40	40	40	40
No NVP	40	40	40	39
Sex of child (male in per cent)				
NVP	59	44	41	46
No NVP	40	71	73	61

Table III *Regression of AA score NVP and smok*
ng status on infant birthweight

Variable	b	p	R^2
AA score before pregnancy	− 82 4	02	046
NVP[1]	148 8	05	072
Smoking status before pregnancy[2]	−127 8	10	085
AA score in early pregnancy	−102 3	31	019
NVP[1]	155 3	04	048
Smoking status in pregnancy	−151 2	07	064

b=regression coefficient (slope) R^2=proportion of variance ex
plained by this and all preceding variables in the equation
p=probability of significance of b taking account of other variables
in the equation
[1] No NVP Some NVP
[2] 0 Nonsmoker 1 Smoker

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URINARY FIBRINOLYSIS IN TOXEMIA OF PREGNANCY

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...stract Serial determinations of urinary plasmin level by ...fibrinocaseinolytic assay were performed in 40 healthy wom... and 29 patients with various types of toxemia throughout pregnancy labor and the puerperium

The results indicate that

1. The urinary plasmin level in normal pregnancy increased significantly from the third trimester to the early puerperium.
2. In mild pre-eclampsia a significant rise in urinary plas...min level from 26 weeks of gestation to the 4th day post partum.
3. In severe pre-eclampsia a progressive decrease in late pregnancy was found After delivery in the early puerperium, the urinary plasmin level of the patients with a rapid ...clinical was significantly higher than that of the patients ...the sequelae of toxemia

Our study showed that serial assays of urinary plasmin activity can provide a reliable and sensitive index of severity, progression and natural history of toxemia of pregnancy.

The term "toxemia of pregnancy" has been applied to the occurrence of various combinations of hypertension albuminuria and edema sometimes further complicated by the development of convulsions and coma, occurring after 20 weeks of gestation These complications make up a confusive complex of related syndromes the etiologies of which have remained obscure despite extensive investigation along many lines The conflict of opinions is not limited to the question of etiology but extends to the practical problems of clinical management

The work of groups under McKay Vassalli ...ender Sheehan and others suggests that toxemia predisposes to a continuing slow state of intravascular coagulation which produces a deposition of fibrin or fibrin like material in the glomeruli (1 9 11 14 15 16 17) In eclampsia the process is massive and sudden and leads to thrombosis of capillary vessels which is visible by light microscopy In pre-eclampsia the clotting is slow and incomplete but progressive and does not lead to the occluson of capillaries but to deposits of macromolecular aggregates of fibrin on the capillary basement membrane which can only be visualized by electron microscopy and immunohistochemical techniques (10 12) McKay and Corey demonstrated that in pre eclampsia the amount of circulating cryofibrinogen was greater than during normal pregnancy labor delivery and the puerperium (7) De Bacalao and Sedlis suggested that an increased platelet adhesiveness in toxemia promoted aggregation and destruction of the platelets in the placenta and other organs (8)

Attention has recently been focused on the fibrin/fibrinogen degradation products (F D P) in blood and urine in patients with toxemia such products being considered a sign of active pathological processes (2 3) But despite much attention to these problems little is known about the urinary excretion of plasminogen and plasmin (urinary P L S) in normal pregnancy and toxemia These may reflect more closely the extent of intraglomerular fibrinolysis in the pathogenesis of pre-eclampsia and eclampsia

In the present study serial sensitive and quantitative assays of plasminogen and plasmin have been used for the detection of intraglomerular fibrinolysis in groups of healthy and toxemic women throughout pregnancy labor and the puerperium

MATERIAL AND METHODS

Forty healthy pregnant women were studied serially from the first trimester to term and during labor and the puerperium with their full informed consent In addition 15 patients with mild pre-eclampsia 7 with severe pre-eclampsia four with abruptio and three with eclampsia were studied Thirty seven healthy non pregnant women ranging from 20 to 30 years of age (mean 24 4 year) and receiving no form of medication were used as controls

For prevention of contaminations from exogenous sources such as blood or discharges from birth canal to compound diagnostic problems Urine samples were obtained by catheterization and prophylactic antibiotics were given to all patients studied

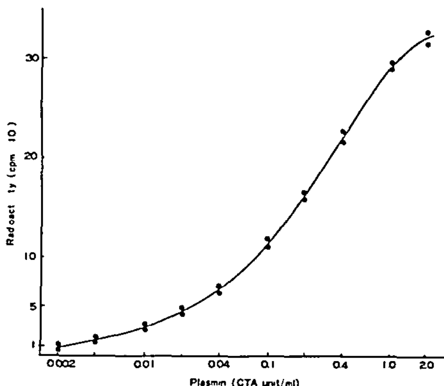


Fig 1 Sta[illegible] [illegible] sine sepharose a[illegible] ma[illegible]ography rad[illegible] assay for plas[illegible]

The urine samples were centrifuged at 3 000 r p m at 4 C and the supernatant was adjusted to pH 7–7 5 and then assayed immediately or stored in aliquots in plastic tubes at –40 C until use

Solid state radioimmunoassay for plasminogen and plasmin antigenicity Anti human plasminogen rabbit serum was prepared by the methods described by Robbins and the IgG fractions were separated by saturated ammonium sulfate solution and chromatography on a DEAE cellulose column (13) The antiserum had the same binding capacity to plasmin and plasminogen Anti plasminogen was labelled with ^{125}I by a method described by Hunter and Greenwood and preparations were obtained with a specific rad[illegible] to 5 μCi per microgram of protein (4) The assay [illegible] microtitre plate technique and gave an accuracy of [illegible] cent As little as 10 μg/l of plasminogen and plasm[illegible] be detected by this method

Lysine Sepharose affinity chromatography ra[illegible]ic assay for plasminogen and plasmin a[illegible] A [illegible] column containing 2 ml mixture of lysine Sepharose and [illegible] labelled casein Sepharose was equil[illegible] ed with 0 [illegible] M P at pH 7 4 Standard plasmin or urine samples were [illegible] to the microcolumn fol owed by washing w[illegible] 0 [illegible] M P two times to remove urinary plasminogen act[illegible]

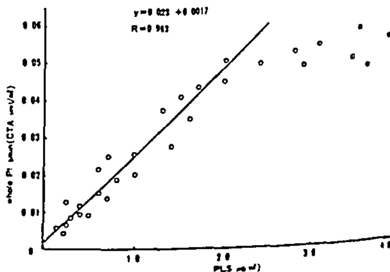


Fig 2 Relation between urinary PLS and whole plasmin in toxemia of pregnancy

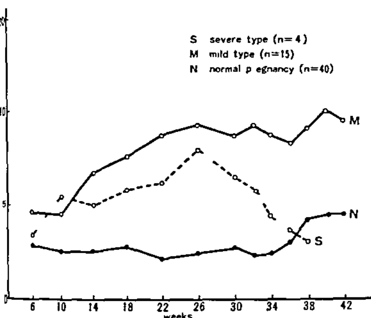


Fig 3 Sequential urinary plasmin studies in normal and toxemia of pregnancy during pregnancy

...inhibitors The column was then incubated at 37 C ... 90 min to digest casein by plasmin affined on lysine ...arose, and to release free [125]I The free [125]I obtained ...s counted for radioactivity The value obtained ...sented the free plasmin activity in urine In order to ...mine the whole plasmin activity plasminogen in the ...ples was activated to plasmin by adding optimal ...ounts of urokinase to the microcolumn The urinary ...e plasmin was defined as the urinary total fibrinolytic ...ivity expressed as plasmin one part of which was ...ginally present in the urine and the other of which was ...verted in the column by urokinase from urinary plas... ...ogen. The sensitivity of the assay method was 0 002 ...AT unit/ml of plasmin (Fig 1)

RESULTS

Plasminogen and plasmin in 33 urine samples from pre-eclamptic patients were measured by using solid ...ase radioimmunoassay and lysine Sepharose affinity chromatography radiocaseinolytic assay in order to correlate the two methods As shown in Fig 2 there was a linear correlation between radioimmunoassay and radiocaseinolytic assay (Y=0 023X+0 0017 ... 0 963) in a concentration of less than 2 μg/ml plasminogen standard

The results of the assay for plasmin in the urine of ... women during normal pregnancy labor and the puerperium are shown in Fig 3 and 4 The urinary plasmin level of 2 7±0 8 CTA unit$\times 10^{-3}$/ml (mean±SD) in early pregnancy was slightly higher than that of 2 1±0 6 found in control groups of non pregnant women No significant alteration of the level took place during the course of normal pregnancy until the third trimester when the mean level rose to 4 9±1 1 a significant increase ($p<0.05$) compared with that in early pregnancy A further increase in plasmin level was found 4 hours before delivery The level reached its peak at 4 hours postpartum and by the fourth day after delivery the mean plasmin level returned to the normal range for nonpregnant women

As shown in Fig 3 urinary plasmin excretion in mild toxemia was significantly higher than in the corresponding stage of normal pregnancy ($p<0.005$) as early as the fourth month of pregnancy The increase in plasmin level persisted during labor and the early puerperium (Fig 4) at a significantly higher level ($p<0.05$) than with a normal delivery group But at the 5th postnatal day plasmin level was in the normal range

In severe pre-eclampsia urinary fibrinolytic activity was elevated in early pregnancy But by the end of the second trimester after the disease had been uncontrolled there was a progressive decrease in the mean value of plasmin Near term the urinary plasmin level fell to a level lower than in the corresponding stages of normal pregnancy (Fig 3)

The severe cases of pre-eclampsia were divided into two groups on the basis of the postpartal clinical

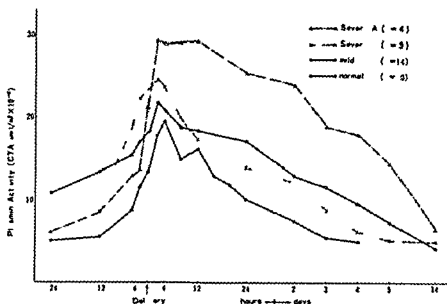


Fig 4 Sequential urinar
min studies in norma
toxemia of pregnancy
labor and the puerpeni

course and the changes in urinary plasmin level (Fig 4) All the patients (4 cases) who showed so rapid a clinical improvement as to become normotensive and free from proteinuria within one month after delivery were classified into Group A A striking rise of urinary plasmin level exceeding that of the normal delivery group ($p<0\ 001$) occurred within 4 to 12 hours postpartum persisted virtually during the first week of puerperium and then decreased gradually during the second week postpartum By the end of the second week urinary plasmin level recovered to a normal or nearly normal value

On the other hand the 3 patients who had t
quelae of proteinuria and/or hypertension one
after delivery were classified into Group B Alt
urinary plasmin level of Group B was slightly el
during the first few days following delivery the
no statistical difference ($p<0\ 05$) in comparison
the normal puerperial subjects

In abruptio placentae urinary plasmin level
strikingly within 24 hours after symptoms app
but after delivery the level sharply decrease
dicating that the free plasmin was quickly elim
from the circulation (Fig 5)

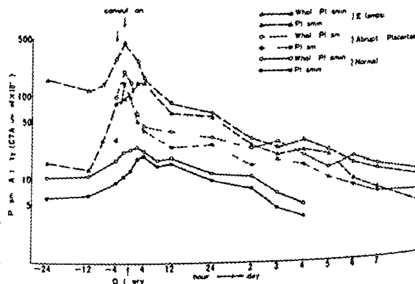


Fig 5 Sequential urinary whole plasmin and plasmin studies in eclampsia and abruptio placentae during labor and the puerperium

In three patients with eclampsia in late pregnancy the whole plasmin in urine increased steeply immediately after the eclamptic seizure of which only a very small proportion was shown to be free plasmin activity indicating that urinary fibrinolytic activity was diminished But a pronounced increase in urinary free plasmin similar to the pattern in the case of abruptio placentae was observed after delivery in the patients with eclampsia

DISCUSSION

Our observations suggest that urinary plasmin activity reflects more closely the extent of intraglomerular fibrinolysis while urinary plasminogen reflects non selective proteinuria in patients with severe toxemia

In the normal healthy kidney only negligible fibrinolytic activity has been found (5) The slight increase in the levels of urinary plasmin during late pregnancy and the early puerperium in normal women are possibly related to the lysis of fibrin in the localized areas of the glomerular compartment (2) An enhanced fibrinolytic activity during labor may be explained by the damage during delivery and could be a natural defence mechanism which maintains the maternal blood supply to the placenta by ensuring the patency of the placental bed during labor (3)

The large amount of urinary plasmin in mild cases of toxemia suggests that active intraglomerular coagulation and fibrinolysis occurred and removed fibrin laid down in the glomeruli lead to a fibrinolysis-dominant state in the urine

In severe pre-eclampsia a marked diminution of urinary plasmin activity in the later part of the gestational period is considered to be an indirect but reliable sign of pronounced renal damage The progressive decrease in the level of urinary plasmin indicated decompensated disseminated intraglomerular coagulation either due to an exhaustion of plasminogen activators or to an increased activity of the fibrinolytic inhibitors in the renal tract Consequently a coagulation dominant picture was brought about in the glomeruli which represents a causative factor in the production of rapid deterioration of renal function during pregnancy Following delivery a striking rise of urinary plasmin level together with rapid clinical improvement in Group A may indicate that a high fibrinolytic glomerular activity in toxemia during the puerperium is a such prognostically favorable sign that the complete evolution and resolution of the glomerular lesion can be expected in this type of toxemia

On the contrary the poor prognosis in severe toxemia of Group B seems to be due to a persistently low activity of postpartal urinary fibrinolysis which leaves intraglomerular lesions may result in residual pro-teinuria and hypertension in this type of toxemia

The very high levels of urinary plasmin found in abruptio placentae may be important in understanding the pathogenesis of the defective hemostasis accompanying this complication and determination of plasmin in the urine could be of great value in the early diagnosis of this obstetric complication

It is of great interest that extremely high levels of urinary plasminogen appeared while urinary fibrinolytic activity remained markedly depressed immediately after the convulsion of eclampsia in late pregnancy However a pronounced increase in fibrinolytic activity during the first two weeks of the puerperium after an eclamptic attack is considered to be a natural healing process of impaired homostasis Some authors have speculated that a toxic substance triggering the clotting mechanism in this disease stimulates aggregation of platelets to form thrombi which were swept into the microcirculation of the brain liver and kidney damaging their vascular endothelium locally and producing alteration of the basement membrane permeability by which red blood cells were forced out into the perivascular region producing the ring hemorrhages found in all patients with eclampsia Such hemorrhages with transient stasis of blood flow in the microcirculation are likely to result in typical acute intravascular coagulation in eclampsia (9 14 17)

The demonstration in this investigation of increased amounts of urinary plasmin suggests that intraglomerular fibrin deposition and fibrinolysis occur in varying degrees in normal parturition toxemia of pregnancy abruptio placentae and eclampsia

The clinical outcomes of these complications of pregnancy probably depends on the balance between clotting and lysis as the condition evolves Finally and perhaps most significantly of all in toxemia of pregnancy the serial estimation of urine plasmin activity may provide a tool which at minimal inconvenience to the patient may be of value in monitoring the progress of the disease and facilitate the continual review of specific therapy (6 18)

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FREEZE MICROSCOPY OF THE ENDOMETRIUM IN ECTOPIC PREGNANCY

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Abstract A series of 60 patients with suspected ectopic pregnancy was reviewed in order to assess the diagnostic value of freeze microscopy of endometrial curettings By this procedure the correct diagnosis has been made in 82 per cent of patients i e it established whether the patient was pregnant and whether the pregnancy was intra or extrauterine

Eighteen patients had an ectopic pregnancy 13 of them were detected primarily on microscopy of frozen sections while the remaining 5 were erroneously classified as non pregnant The diagnostic sensitivity of freeze microscopy proved to be equal to microscopy of the subsequent paraffin sections

A diagnostic and therapeutic schedule can be set up for patients with suspected ectopic pregnancy when the histological appearances of the frozen sections and the result of the HCG reaction are known

The best known early gestational changes in the endometrium are the presence of decidua and the Arias Stella phenomenon (11 12) which is defined as the occurrence in endometrial glands of cells having an enlarged irregular hyperchromatic nucleus and pale vacuolated cytoplasm (1)

A somewhat less known morphological sign of pregnancy is the gestational hyperplasia described by Hertig in 1964 (6) This is the simultaneous presence in the endometrium of secretion stromal edema and predecidua three phases which occur sequentially in the non pregnancy menstrual cycle

The Arias Stella phenomenon has been observed as early as the 22nd day after the first day of the last menstrual period (7) and gestational hyperplasia develops from the 23rd – 28th day of the cycle In other words these histological characteristics afford a possibility of a very early diagnosis of pregnancy including its ectopic variant

In the Gynecological/Obstetrical Department of the Central Hospital Slagelse the ordinary clinical examination for ectopic pregnancy has been supplemented since 1971 by microscopic examination of frozen sections of endometrial material obtained by curettage or vacuum curettage However this method has only been used when the ordinary clinical examinations have not been able to prove or disprove a suspicion of ectopic pregnancy and the patient did not wish to continue a possible intrauterine pregnancy

Accordingly the patients in the present series make up only a small part (about 20 per cent) of the total number admitted to the Department with a suspicion of ectopic pregnancy during the period under study Patients having classical acute symptoms and signs of ectopic pregnancy were initially subjected to laparotomy or laparoscopy Only patients giving rise to diagnostic difficulties and having metrorrhagia menostasis and/or unilateral parametrial masses have had frozen section microscopy of the endometrium and were included in the present material

PRESENT INVESTIGATIONS

Material The series is composed of 62 patients admitted during the period 25 8 71 – 29 11 77 However one patient entered the series twice and two were excluded one because the curettings did not yield any tissue for a histological diagnosis and the other because the final clinical diagnosis remained uncertain (a regressed tubal abortion could neither be excluded nor confirmed) This leaves 60 patients in whom clinical examination initially gave rise to a suspicion of ectopic pregnancy without there being any indication for acute laparotomy or laparoscopy

Table I gives the diagnoses on admission

Table I *Diagnoses on admission*

	No of pat s
Induced abortion	14
Threatening abortion incomplete abortion or spontaneous abortion	14
Suspicion of ectopic pregnancy	24
Other diagnoses (metrorrhagia ovarian cyst acute appendicitis etc)	8

Table II Relationship between frozen section microscopy and clinical diagnosis

	Clinical diagnosis		
	Ectopic pregnancy	Intrauterine pregnancy	Not pregnant
Frozen section microscopy			
Ectopic pregnancy	13	3	2
Intrauterine pregnancy	0	24	1
Not pregnant	5†	0	12
Total	18	27	15

† Re false negative frozen section microscopy cf Table III
Re false positive frozen section microscopy cf Table IV

Method In 30 cases the endometrial specimens were obtained by vacuum curettage using the Vabra aspirator® thus avoiding general anesthesia (unless in certain cases) and dilatation of the cervical canal The remaining procedures were done by a conventional curette or else as a vacuum evacuation if the patient had been referred primarily for an induced abortion

The material was sent immediately unfixed to the Department of Pathology where the tissue (as a rule *in toto*) was frozen cut into 8–10 µm sections in a cryostat and stained with toluidine blue/eosin as described by Henriques (5)

In all cases the histological diagnosis was obtained within 20 minutes As detailed below it was designated positive if it was not intrauterine pregnancy (pregnancy product) or non pregnant The subsequent procedure (laparoscopy laparotomy or further observation) was decided on basis of the microscopic findings and clinical appear Twenty nine patients had laparotomy or laparoscopy a continued suspicion of ectopic pregnancy All the others were followed until the clinical diagnosis had been fully established Patients diagnosed as spontaneous abortion or incomplete abortion' were designated as having intrauterine pregnancies if according to the clinical findings the abortion was assumed to have occurred not earlier than one month before the freeze microscopy

RESULTS

Among the 60 patients the correct diagnosis was made by frozen section microscopy in 49 (=82 per cent) (95 per cent confidence limits 69 6 per cent – 90 5 per cent) The results are presented in Table 2

In 18 patients the ectopic pregnancy was confirmed at operation 13 of them had been diagnosed by frozen section microscopy (=72 per cent) (confidence limits 46 5 per cent – 95 3 per cent) In the false negatives neither the frozen sections nor the final paraffin sections showed any signs of pregnancy

In 5 patients who did not have an ectopic pregnancy the diagnosis after microscopy of the frozen sections had been possibly ectopic pregnancy'

Tables 3 and 4 give the relationship between the histological findings on frozen sections on paraffin sections and the final clinical diagnosis in the false reports

DISCUSSION

In previous studies on the diagnostic value of histological examination of endometrial tissue f possible ectopic pregnancy the diagnostic criterion ectopic pregnancy has been mainly the occurrence the Arias Stella phenomenon without the simultaneous presence of placental components or fetal tiss

Table III Relationship between frozen section microscopy and paraffin section microscopy in patients whom the frozen sections had shown no pregnancy but in whom clinical examination revealed ectopic pregnancy i e the false negatives

No of pat s	Diagnosis on frozen section microscopy	Diagnosis on paraffin section microscopy
7	Endometrium with necrotic tissue—placental remnants?	Endometrium in proliferative phase with signs of bleeding Flakes of necrotic tissue
15	Suspicion of dyshormonal endometrium predominantly in secretory phase	Dyshormonal endometrium of secretory type No signs of pregnancy
21	Endometrium without signs of pregnancy	Endometrium in uncharacteristic phase
32	Endometrium in secretory phase with localized decidual stromal reaction	Endometrium in menstrual phase No signs of pregnancy
35	Endometrium in proliferative phase	Endometrium in proliferative phase No evidence of pregnancy

ble IV Fro en section diagnosis paraffin section diagnosis and final (clinical) diagnosis in patients who d been erroneously diagnosed on freeze microscopy as (possibly) ectopic pregnancy

t. no	Frozen section diagnosis	Paraffin section diagnosis	Final (clinical) diagnosis
	Decidual endometrium E top c pregnancy cannot be excluded	Villi demo istrable Pregnancy products	Intraut rine pregnancy
	Secretory endometrium and ample decidua Ectop c pregnancy cannot be excluded	Decid a with occasional small particles of trophoblast	B corn ate uteru curetted in non-p egnant horn Lapa.oscopy
	Endomet ium with characteristics of pregnancy (no pregnancy products)	Dyshormonal endometriu n with localized dec dua Endometrit (seq to pregnancy)	Pvosalpinx non pregnant induced abort on 5 weeks p eviously Operat on
	Endometrium with decidua and Arias Stella phenomenon	Endometrium with characteri tics of pregnancy (no pregnancy produ t)	Spontaneous abortion a. home
	Mild Arias-Stella phenomenon and and se ere p edec dual reaction Possibly pregnant	Dyshormonal endometrium Possibly pregnant	Metrorrhagia Not p egnant Operat on

This criterion has been fulfilled in about 70 per t of the patients with confirmed ectopic pregnancy practically all studies (2 3 4 8 9 10) In the re ining 30 per cent it has not been possible to find inite signs of pregnancy in the endometrial tissue sumably because of the death or insufficiency of gestational tissue in respect of hormone produc d prior to the time of curettage Owing to this large number of false negatives microscopic examination f the endometrium on suspicion of ectopic pregnan y has rarely been used Its applicability has been fur her restricted by having to wait 24—28 hours—with the conventional histological technique—for the mic roscopic diagnosis

The use of freeze microscopy does not appear to have been reported previously in this connection

In the Department of Gynecology/Obstetrics in the Central Hospital Slagelse frozen section microscopy of the endometrium has proved to be a rapid reasonably easy and valuable method This applies particularly when the material has been obtained by the Vabra aspirator R and without the need for a.esthesia It is remarkable that the frozen section method has proved to be as sensitive as the conven tional method using paraffin sections Like others before us we must admit that about 30 per cent of the ectopic pregnancies were not recognized by microscopic examination of the endometrium pre sumably owing to insufficient secretion from the ec topic gestational site and a resulting lack of endome trial reaction viz the Arias Stella phenomenon and/or gestational hyperplasia

Should the use of frozen section microscopy of the endometrium come into wider use in cases where the diagnosis of ectopic pregnancy is in doubt we feel that we can recommend the following guidelines

(1) If microscopic examination of frozen sections reveals intrauterine pregnancy the suspicion of ectopic pregnancy must be considered to have been dis proved The diagnosis of intrauterine pregnancy is based upon the demonstration of placental components and/or fetal tissue in the curettings which is not difficult in frozen sections (Indeed our series does not include any patients with ectopic pregnancy who have been diagnosed as having intrauterine preg nancy) Such patients (who made up 42 per cent our series) can be immediately discharged for continued out patient follow up unless this is contra indicated by other diseases This is in an essential advantage especially when the suspicion of ectopic pregnancy has arisen in connection with an out patient procedure for induced abortion

(2) If the frozen section microscopy gives rise to a suspicion of ectopic pregnancy (i e shows the Arias Stella phenomenon and/or gestational hyperplasia without the presence of fetal or p lacental com ponents) this is an indication for immediate laparos copy or laparotomy in 30 per cent of our patients In our series 72 per cent of these patients proved to have ectopic pregnancy

(3) This leaves 17 patients (28 per cent) in whom frozen section microscopy showed no signs of preg nancy Three of these cases had a positive urinary HCG reaction If the HCG is positive laparoscopy should be carried out as the microscopic report no signs of pregnancy practically rules out an in trauterine pregnancy Ectopic pregnancy was found in two of our three patients in this group The

patient had a positive HCG reaction on admission but the reaction changed to negative during her stay in hospital Thirty four days before admission the patient had undergone induced abortion (which showed fetal components) and the post abortion course had been complicated by long lasting metrorrhagia On the basis of the positive HCG reaction laparoscopy was performed but did not show any signs of an ectopic pregnancy

In our opinion patients with a frozen section microscopic report of no signs of pregnancy and a negative HCG reaction but with a continued clinical suspicion of ectopic pregnancy should be kept in hospital and observed In our series this applied to 14 patients (23 per cent of the whole series) 3 (21 per cent) of whom proved to have ectopic pregnancy In such cases the further procedure must be based upon the clinical state

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HYDROP DEGENERATION

A histopathological investigation of 260 early abortions

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Abstract Placental tissue from 160 abortions provoked during the 6th – 12th weeks and 100 spontaneous abortions between weeks 5 and 16 were studied histopathologically in respect of a comparison and quantitation of hydrop degeneration

Significantly more cases of severe hydrop degeneration were observed among the spontaneous abortions ($p < 0.001$) Of these abortions 87 per cent were hydrop degenerated to varying degrees 41 per cent were severely hydrop degenerated Among the provoked abortions approximately 81 per cent were hydrop degenerated to varying degrees but only 6 9 per cent were severely hydrop degenerated The relationship between severe hydrop degeneration and chromosome abnormality is discussed

Hydrop degeneration of the chorion villi is a common histological finding in placentae from early (1st trimester) abortions and it is a normal finding in a small area between the chorion leave and chorion frondosum (5 8) In addition a strong correlation has been demonstrated between chromosomal abnormalities in the aborted tissue and hydrop degeneration (2, 9 12 13 18)

A considerable variation in the severity of placental hydrop degeneration has been observed during routine examination of tissue from both early spontaneous abortions as well as early provoked abortions Thus routine examination has revealed placentae with only a few hydrop-degenerated villi as well as placentae in which an overwhelming majority and in a few cases all the villi were hydrop degenerated Despite this the authors shown in Table I have not quantitated their findings of hydrop degeneration This has given rise to considerable variation in the incidences quoted The object of the present investigation had been partly to quantitate hydrop degeneration in the chorion villi from early placentae and partly to compare the findings from spontaneous and provoked abortions

MATERIAL AND METHODS

The material comprises placental tissue from 100 early spontaneous abortions and from 160 abortions provoked during the 1st trimester The investigation is consecutive except that preparations with less than 800 chorion villi were excluded

All the abortions took place in the latter half of 1976 in the Obstetric Department of Odense University Hospital

No prostaglandin or saline induced abortions are included in the material

The average gestational age of the spontaneous abortion was 11 weeks (range 5 – 16 weeks) and of the provoked abortions 9 weeks (range 6 – 12 weeks)

The age distribution of the women is shown in Fig 1 The average age of those with spontaneous abortion was 27 6 years and of those with provoked abortion 27 2 years None of the women occur more than once in the material

The placental material was fixed for at least 24 hours in 10 per cent buffered formalin whereafter 2 – 6 capsules were filled with tissue for embedding in paraffin Thereafter

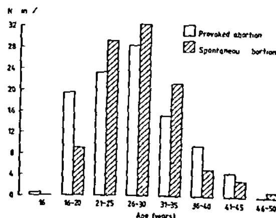


Fig 1 The number of women in the various age groups Note that approximately 50 per cent of the provoked abortions were carried out on women in the age group 20 – 30 years and that approximately 60 per cent of the spontaneous abortions occurred within this age group Only one of the 160 women subjected to provoked abortion was below the age of 16 years

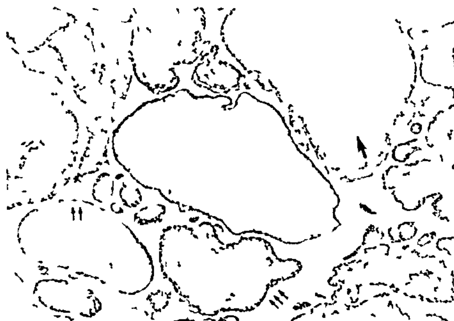


Fig 2 Hydrop degenerati of grade I Only a few of t chorion villi have vacuoliz and edematous mesobl (one arrow) and narrowe single layered trophobl (two arrows) Further m the absence of vessels in the villi Normal chorion vil (three arrows) with loose st ma and double layered t phoblast (×100)

the tissue was cut into 6 μ thick sections and routinely stained with hematoxyline eosin for light microscopic examination Typical hydrop-degenerated chorion villi have edmatous vacuolated mesoblast The blood vessels are small or completely absent The structures of the chorion villi are often smoothed with a narrow single layered trophoblast (see Fig 3)

The quantitation of the hydrop degeneratin was carried out as follows

Grade 0 Less than 1 per cent hydrop-degenerated chorion villi per placenta

Grade I 1–20 per cent hydrop-degenerated chorion villi per placenta

Grade II 21–40 per cent hydrop-degenerated chorion vi per placenta

Grade III More than 40 per cent hydrop-degenerat chorion villi per placenta

RESULTS

The distribution of the hydrop degeneration respect of severity corresponding to provoked an spontaneous abortions is shown in Table 2 It m be seen that only 18 6 and 13 per cent of the examine



Fig 3 Hydrop degeneration of grade III Large edematous and vacuolated chorion villi which in several places are covered with single layered trophoblast (one arrow) The majority of the chorion villi have no vessels though a villus with hypoplastic vessels can be seen (two arrows) (×150)

Table I *Some earlier studies on the incidence of hydrop degeneration in spontaneous abortions*

Author and Year	Incidence in per cent
Gray (1957)	2 7
Dedowic and Pisarki (1967)	10
Novak (1968)	14
Javert (1957)	18
Eckmann and Carrow (1962)	29
Mall and Meyer (1921)	31 5
Huber Mellin and Vellios (1957)	40
Abaci and Aterman (1968)	41 3
Ecke Bailo and Finzi (1969)	52 5
Upadhyay Prakash and Singh (1967)	60
*Hertig and Edmonds (1940)	66 9

among pathological ova

placentae respectively were found to have less than 1 per cent hydrop-degenerated chorion villi Forty one per cent of the placentae from the spontaneous abortions had severe hydrop degeneration compared with only 6 9 per cent of those from the provoked abortions ($p<0\ 001$) The hydrop-degenerated chorion villi either lay in small clusters or were spread diffusely throughout the placental tissue (Fig 2 grad I Fig 3 grade III)

No qualitative difference was observed between the hydrop degeneration in the spontaneous and provoked abortions In the great majority of cases the hydrop-degenerated villi were without blood vessels or the blood vessels were hypoplastic

No abnormal trophoblast hyperplasia was observed on the contrary the trophoblast layer appeared thinner than usual and often consisted of only a single row of cells in the swollen and edematous villi Fig 3)

DISCUSSION

It can be seen from Table 2 that hydrop degeneration of varying degrees is present in 87 per cent of the placentae examined from spontaneous abortions and in 81 4 per cent of those from provoked abortions

These figures are somewhat higher than those reported previously (Table I) However the studies referred to in the Table give no quantitation of the hydrop dengeration and it is therefore extremely difficult to make any comparison either between the incidences stated in the various publications or between these and the present findings The reason for this is that much will depend on the individual author s ideas as to how many chorion villi must be hydrop degenerated in a placenta before this is classified as hydrop degenerated

In addition to these purely quantitative problems there are a number of qualitative questions which are still unsolved Thus some authors distinguish between hydrop degeneration without trophoblast hyperplasia and hydatidiform degeneration with trophoblast hyperplasia (20) No abnormal trophoblast hyperplasia was observed in the present study neither was there any case with clinical or histological evidence of a hydatidiform mole Further other authors only make the diagnosis hydrop degneration if macroscopic examination with the naked eye of the aborted tissue discloses vacuolated chorion villi In addition to these problems of definition there were difficulties in earlier investigations in determining whether an abortion was in actual fact spontaneous or criminal (17) It has been possible to ignore this problem in Denmark because free abortion became a legal right as of October 1973 so that the number of criminal abortions since then is no doubt extremely low

It would be desirable to have both a quantitative and a qualitative standardization of the criteria for hydrop degeneration as in particular the studies of the last 10–15 years of immature placentae have shown a strong correlation between hydrop degeneration and abnormal chromosomes in abortion tissue Thus Honore *et al* using light microscopic evaluation of placentae have been able to predict chromosome abnormality with considerable accuracy

It can be seen from Table 2 that the number of hydrop-degenerated chorion villi is much the same in

Table II *The incidence of hydrop degeneration of various degrees of severity in placental tissue from provoked and spontaneous abortions The figures in brackets are percentages*

	Grade (hydrop degeneration)				Total
	0	I	II	III	
Provoked abortions	30 (18 6)	92 (57 5)	27 (16 9)	11 (6 9)	160 (100)
Spontaneous abortions	13 (13 0)	37 (37 0)	9 (9 0)	41 (41 0)	100 (100)
Total	43 (16 5)	129 (49 6)	36 (13 8)	52 (20 0)	260 (100)

spontaneous and provoked abortions until approximately 40 per cent of the placenta is involved It is only after this stage (grade III) that a sharp rise occurs in the number of hydrop-degenerated placentae in spontaneous abortions (chromosome abnormality?) Thus hydrop degeneration of grade III is found significantly more frequently among spontaneous abortions than among provoked It can further be seen from Table 2 that a lower degree of hydrop degeneration (grades I and II) is exceedingly common and therefore in all probability a harmless phenomenon in early placentae from both spontaneous and provoked abortions

An investigation regarding a possible correlation between chromosome abnormalities and the histopathology of abortion tissue is under preparation in our laboratory

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INFERTILITY FACTORS

Their relative importance and share in an unselected material of infertility patients

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bstract A 7 year material of 196 infertile couples is pres
ted 1 5 – 8 5 years after investigation and/or treatment
r infertility rather more than 48 per cent of the women
ad conceived and of these pregnancies 19 per cent ended
abortion

Various factors such as duration of infertility age
story of pelvic inflammatory disease and previous use of
al contraceptives are analyzed for their relative share in
e material and relative importance for the chances of
—Unlike age the duration of infertility was an
portant prognostic factor also when it exceeded 2 years
evious operations on the internal genitalia reduced the
ances of conceiving essentially more than a history of one
isode of pelvic inflammation whereas several episodes of
lvic inflammation seemed to spell an equally unfavorable
ognosis As expected infertility caused by oral contra
ptive-conditioned oligo-amenorrhea was considerably
sier to treat than other forms of infertility Oligo-amenor
ea was significantly more common among patients who
d used oral contraception for 1 – 6 years than among
ose who had used it for less than 1 year —The incidence
abortion in patients with secondary infertility was about
ree times higher before than after the infertility investiga
ons

Lastly the individual infertility diagnoses were analyzed
the same way as regards relative share and importance
bout 42 per cent of the operated patients succeeded in con
iving It is remarkable that 8 patients had a bicornuate
erus and of them 7 had oligo- and/or hypomenorrhea

everal factors are involved in human reproductive
bility The percentage share of unknown factors
mong infertile couples has ranged from 5 – 20 per
ent (4 6) In materials in which an attempt has been
ade to assess the frequency of a multifactorial
tiology up to 45 per cent (3) have proved to belong
o this category Therefore it may be difficult in
any respects to set up applicable prospective and
ontrolled studies to elucidate the influence of in
ividual factors upon infertility The object of the
resent study was to analyze an unselected material of
nfertile couples investigated and treated for the infer
tility especially with reference to the fertility
educing effect of the individual factors

MATERIAL AND METHODS

During the 7 year period from 1 1 1967 to 31 12 1973 a total of 196 women including 4 previously sterilized were admitted to the Gynecologic Department of the Central Hospital Naestved for investigation and treatment of infertility Only 14 (7 1 per cent) did not want further investigations after the first consultation The analysis was done by collecting data from the case records and from questionnaires Twenty five patients (12 8 per cent) could not be traced The analysis was terminated in the autumn of 1975 so that the follow up period ranged from 1 5 to 8 5 years

Fig 1 sets out the distribution by age and by primary and secondary infertility 56 8 per cent applied because of primary and 43 2 per cent because of secondary infertility 77 6 per cent of the patients were under 30 years of age when first seen Eleven patients (5 5 per cent) were over 35 years and of this group 6 were applying because of primary infertility In almost one-quarter of the patients the duration of infertility was 1 – 2 years in almost one half from 2 – 4 years and in almost one third more than 5 years

The majority of the patients a total of 128 were admitted during the initial diagnostic work up and thereafter attended as out patients for continued investigations and/or treatment Twenty nine patients had previously been investigated and treated for infertility

As a routine general clinical and gynecological examinations were performed The anatomical condition was assessed by hysterosalpingography (HSG) In 16 cases HSG was not performed because in 10 patients the wish to conceive was not so ardent or because the patient refused this examination Two conceived before the radiography was done and in four HSG was omitted because the patients had previously been sterilized

The presence of ovulation was assessed primarily by basal temperature curves through 2 or 3 months In the meantime some of the patients conceived Measurement of total estrogens and pregnandiol in the 24-hour urine and endometrial biopsy were done in rather more than half the patients Other investigations for endocrine status including determination of pituitary gonadotropin adrenocortical and thyroid function parameters were carried out when this was felt to be indicated

No attempt was made to assess the role of the cervix factor in infertility as detailed studies of this factor were not initiated until the early 1970 s However a few patients in whom cervicitis was the only abnormal finding were assigned to this group

Investigations of semen were carried out in the laboratory

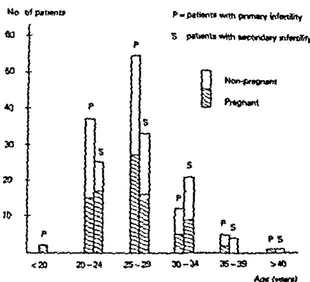


Fig 1 Conception rate by age for patients with primary and secondary *infertility* respectively

of the Central Hospital Thirty five refused to have this investigation or postponed it so that several of the women had conceived *in* the meantime In 13 cases *the* reason why the husband s sperm was not studied is not stated In cases of male infertility the husband was referred to an andrologist for *special* treatment

RESULTS

Of the total *material* of 196 patients 94 *or* 47 7 per cent conceived Eighteen or 19 1 per cent aborted ...uming that the *25 patients* who could not be traced had the same conception rate as those who could be followed the conception rate in the total series is 54 6 per cent Below the rate will be given *mostly* without this correction *and* is thus a minimum value When the rate is followed by a figure in brackets the correction has been made Of the 111 patients with primary infertility 52 or 46 8 per cent conceived and of the 85 with secondary *infertility* 42 or 49 4 per cent The difference is not statistically significant (chi square test $p > 0\ 05$) The duration of *infertility*

Table I *Influence of duration of infertility upon conception rate*

Duration of infertility	No of patients	No and percentage who conceived
1–2 years	44	33 (75 0)
2–4 years	108	52 (48 2)
>4	44	9 (20 3)

the figures within parentheses denote numbers in per cent

Table II *Abortion rate for patients with secondary infertility before and after investigation and/or treatment for the infertility*

	Before investigations for infertility	After investigations for infertility
No of pregnancies	112	41
Abortions	32 (28 8)	5 (12 2)

the figures within parentheses denote numbers in per cent

seemed to be longer for the *patients* with primary infertility than for *the secondary* cases a duration of less than 4 years being *found* in 71 = 64 per cent and 64 = 75 per cent respectively However this difference is not *significant* (*chi square test* $p > 0\ 05$)

The *duration of infertility* is correlated to the conception rate in Table I *It is* apparent that the conception *rate* falls with increasing duration of infertility The differences are statistically significant between all three groups (chi square test $p < 0\ 01$) The mean duration of infertility for *those* who conceived and for *those* who did not was calculated as 2 1/4 and 4 years respectively The respective 95 per cent confidence limits are then 2 0–2 5 years and 3 5–4 5 years (SEM_1 0 17 and SEM_2 0 25)

The *influence* of *age* upon the chances of pregnancy may be *seen* from Fig 1 Analysis of the differences between the 5 year groups showed no statistical significance

In the analysis of the collected anamnestic data, particular interest was taken in a history of abortion of operations on the *internal* genitalia of pelvic inflammatory disease and of the use of oral contraceptives

A *history of spontaneous abortion* in patients with secondary infertility was elicited in 32 out of a total 112 pregnancies = 28 8 per cent (95 per cent confidence limits 20 9–38 6 per cent) After the investigations and treatment for infertility the same patients obtained 41 pregnancies 5 = 12 2 per cent of which terminated *in* abortion (The calculations do not include patients who had previously been sterilized) This difference in the abortion rate before and after the investigations *for* infertility is *significant* (*chi square test* $p < 0\ 05$) cf Table II — The duration of infertility and the time of *conception after* the investigations had been completed was compared for patients with and *without* a history of abortion (*Table III*) with a view to possibly demonstrating a lower fertility in the former group No such finding is

Table III *Duration of infertility and time of conception after investigation and/or treatment of patients with a history of abortion and patients who had no such history*

	Duration of infertility (years)			Time of conception (years)		
	≤2	>2<4	≥4	≤2	>2<4	≥4
Pats with a history of abortion (3)†	9 (28 1)	14 (43 8)	8 (25 0)	14 (77 8)	2 (11 1)	2 (11 1)
Pa..s with no history of abortion (164)	35 (1.3)	76 (46 3)	53 (3..3)	60 (78 9)	13 (17 1)	3 (3.9)

the figures ithin parentheses denote numbers in per cent
† the figures within parentheses denote number of patients

apparent from the table but it shows a shorter duration of infertility among patients with a history of abortion

A history of *extrauterine pregnancy* was reported by 5 patients = 5 9 per cent In all of them one Fallopian tube had been excised Three of the patients with a normal remaining tube at HSG conceived and delivered The other two had sactosalpinx and did not conceive

Fifteen patients had a history of *operation on the internal genitalia* (this does not include the four who had undergone sterilization) At HSG 7 of these patients or 46 7 per cent had obstruction to passage in both tubes and 5 or 33 3 per cent succeeded in conceiving Within the remaining part of the material bilateral tubal occlusion was found in 38 cases = 20 3 per cent The differences in the occurrence of bilateral tubal occlusions and in the conception rates between the group with a history of operation on the internal genitalia and the remainder of the material are statistically significant (chi square test $p < 0\ 05$)

Among other anamnestic data which may be of causal importance to infertility there is a history of *pelvic inflammatory disease* Such a history was elicited in 57 or 29 1 per cent one episode in 35 of them and two or more episodes in 22 Twenty-eight or 48 3 per cent achieved pregnancy which does not indicate a poorer prognosis for patients with a history of pelvic inflammation than for the remainder of the material From Table IV it is apparent that patients with a history of one episode of pelvic inflammation had the same chances of conceiving as the other infertility patients On the other hand repeated pelvic inflammations impair the chances of pregnancy but only in the presence of tubal occlusion on the HSG However the difference in the conception rate between these two sub-groups is not statistically significant (Fisher s exact test $p > 0\ 05$) In more than half of both sub-groups or more accurately in 20 and 12 patients with a history of one and of several episodes of pelvic inflammation the tubes were normal at HSG and in these patients the conception rate was the same as in the other infertility patients

Table IV *Presence of tubal occlusions and conception rate in infertility patients having a history of one or more episodes of pelvic inflammatory disease*

No of episodes of pelvic inflammatory disease	Tubal occlusions			Conceived
	Partial	Total	In all	
One episode (35)†	7	8	15 (4..8)	7 (46 7)
Two or more (22)†	4	6	10 (45.5)	1 (10 0)

the figures w thin parenthesis denote number in per cent
† the figures within parenthesis denote number of patients

Seventy six patients or 38 8 per cent of the total material had used *oral contraceptives* for up to 6 years 40 of them for less than one year 25 for 1−2 years 10 for 3−4 years and one patient for 5−6 years — To assess the importance of previous oral contraception as a cause of infertility the use or non use of oral contraceptives is correlated in Table V with major HSG findings with bleeding disturbances at the time of the first visit and with the conception rate A comparison of patients who had not used oral contraception with patients who had used the Pill for a short time and patients who had used it for a long time shows in this sequence a fall in the frequency of abnormal HSG with tubal occlusions and an increasing frequency of bleeding disturbances in the form of oligo- and amenorrhea at the first consultation The differences in the frequency of tubal occlusions and the occurrence of oligo- and amenorrhea between users and non users of contraceptive pills are statistically significant So is the difference in the frequency of oligo- and amenorrhea between patients who had used oral contraception for less than one year and patients who had used it for 1−6 years (square test $p < 0\ 05$) From the same table it

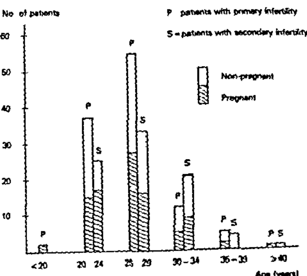


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Table VII *Types of surgery*

Type of surgery	No of pat s	No who conceived	No of years after surgery 0–1	1–2	2–4	>4
Bilateral salpingostomy	17	3	1		2	
Unilateral salpingostomy	5	2	2			
Unilateral salpingectomy	5	2				2
Reimplantation of tubes (after sterilization)	4	1				1
Detachment of adhesions	4	2	2			
Ovarian resection	4	4	2	2		
Myomectomy	3	2		1		1
Ventrosuspension of the uterus	9	5	3	2		
Strassman s operation	1	1	1			
Total	52	22	11	5	2	4

the first year after the treatment Another 12 patients were treated with Clomivid[R] because the basal temperature curves indicated questionable ovulation On this treatment 90 per cent exhibited definite ovulation and 80 per cent conceived the majority within the first year after the treatment

Abnormalities of the *semen* as the only cause of infertility were demonstrated in only 19 or 9 7 per cent of the cases Pregnancy was obtained in 8 = 42 1 per cent The small number in which male infertility was the only cause is explicable partly by the large number of husbands who refused to have the analysis Among the 36 cases of unknown cause of infertility 10 of the husbands had not been examined Further investigation of these 10 patients data showed that on the whole their motivation for the investigations was slight

In 26 patients or 13 3 per cent the diagnostic programme revealed *multiple diagnoses* This number would presumably have been larger if a more consistent study had been made of the role of the cervix factor and if laparoscopy had been done to disclose endometriosis and adhesions around the internal genitalia Such changes are frequently not detected at HSG Information about the husband s semen was lacking for 5 patients in this group

It is remarkable that in 7 patients with oligo-and/or hypomenorrhea HSG showed a slightly bicornuate or a unicornuate uterus None of the patients without oligo- or hypomenorrhea had any form of uterine developmental anomaly except for one who underwent a Strassmann operation In this patient the bleeding pattern was completely normal Within the total series 65 patients had miscellaneous bleeding disturbances when first seen This includes 38 with oligo- or amenorrhea and 3 with hypomenorrhea There was a statistically significant difference in the occurrence of bicornuate and unicornuate uteri among these types of bleeding disturbances compared with the remainder of the infertility patients (chi square test $p < 0.01$) Table VIII gives the bleeding intervals and the previous use of oral contraceptives for the above mentioned 7 patients Hormone analyses including thyroid parameters were normal in all

Table VIII *Data for patients with bicornuate uterus and oligo- or hypomenorrhea*

Age (years)	History of previous delivery	History of previous abortion	Had used oral contraceptives	Intervals between menstrual periods	Hypomenorrhea	+/− ovulation
23	+		1–2 months	4–8 weeks	+	+
24	+		12	8–24		−
25	+	+	−	2–6		+
25			6	4–8		+
26			24	4–12		+
30			24	4–8	+	+
32	+	+	6–8	4	+	+

7 In one patient however the hormone analyses were not complete — In 5 of the 6 patients who had *previously used oral contraceptives* the bleeding disturbances had started before she began using this form of contraception

Out of the total of 94 patients who conceived after investigation and/or treatment 55 or 58 5 per cent had conceived within one year 19 or 20 2 per cent within 2 years 15 or 16 0 per cent within 4 years and 5 or 5 3 per cent later Among the 102 patients who did not conceive 52 stated at the time of follow up that they no longer wanted to become pregnant Eighteen reported having adopted children

DISCUSSION

The present infertility material does not differ essentially from most others with respect to age primary and secondary infertility percentage completing the diagnostic work up and tracing percentage (1 4 6 8 9 11) In most studies as here the infertility limit has been set at 1 year s involuntary childlessness partly because in almost 90 per cent of fertile couples conception occurs within 12 months (16) partly because it cannot be expected that the chances of conception increase with time in certain cases of absolute infertility On the other hand differences in the length of the follow up period in the various analyses of infertility materials can essentially influence the values for the prognostic results, but cannot reduce the comparability as regards the relative share of the individual infertility factors and the role of fertility suppression The present patients must also be presumed to have been largely unselected as there was no primary gynecological service in the area at the time However it may be imagined that in a few cases in which the patient s own doctor has found aspermia or considerably reduced fertility in the husband the case has been referred directly to an infertility clinic with andrological sub speciality

There was no definite difference in the conception rate between primarily and secondarily infertile patients Yet there has been a general trend to a somewhat better prognosis for secondary infertility in the various studies although in most material the differences have not been significant (1 3 9) Only Southam & Buxton (11) found a significant difference This may indicate a real difference in fertility between the two groups but the explanation could also be that the secondarily infertile patients have a shorter duration of infertility presenting themsel earlier partly because of an older mean age and partly because of a possible tendency to abortions L De George & Nesbitt (3) we found a shorter duration of infertility among the patients with secor in those with primary infertility In general this is tantamount to a higher conception rate as is apparent from Table I

The marked fall in the conception rate when duration of infertility increases from 1 to 2 years or more agrees with previous findings (1 6 9 11) Also a further sub-division of durations of infertility past 2 years often shows a continued decrease in the conception rate However there do not seem to be other studies demonstrating—as here—a significant difference between the groups whose infertility exceeds 2 years (Table I) This *per se* renders the duration of infertility an important factor in the reproduction potential As a result it is more difficult to doubt the infertility problem in patients with less than 2 years infertility as Southam & Buxton (11) do —The significant difference in the median duration of infertility between patients who achieve pregnancy and those who do not agrees with the findings of De George & Nesbitt (3)

The effect of age on infertility has been investigated just as often as the influence of the duration of infertility Several authors have found a decreasing fertility, in terms of achieved pregnancies with increasing age (1 6 8 11) Studies in which an attempt has been made to correct for the partial incorporation of age in the duration of infertility have shown like ours no influence of age upon the chance of conception (3 4)

A 2 to 4 times higher abortion rate among with low fertility or infertility compared with normally fertile women has been substantiated only a few times previously in similar materials Southam (11) found in accordance with the present study a decrease in the tendency to abortion after investigation and treatment for the infertility When the fertility increases the abortion rate decreases However the fertility in patients with a history of abortions does not increase to the extent of being reflected in the time of conception after investigation and treatment for the infertility in relation to other infertility patients (Table III)

It has previously been demonstrated that a history of operations on the internal genitalia is tantamount to decreased chances of conception (7) The prognosis for these patients is essentially poorer than for

other infertility patients Between the two groups there is a significant difference in the occurrence of bilateral tubal occlusions which *ceteris paribus* is an unfavorable infertility diagnosis as regards treatment

About 30 per cent of the present patients had a history of pelvic inflammatory disease once or several times According to our study this group as a whole does not have a poorer prognosis than the other patients It was only in cases with a history of several episodes of pelvic inflammation and at the same time tubal occlusions at HSG that the chances of pregnancy were reduced Lamb (7) who made no distinction between patients with one or more episodes of pelvic inflammation found a tendency to poorer chances of pregnancy in the total group but was unable to draw definite conclusions because the material was too small

To assess the role of oral contraception in an ordinary unselected infertility material the frequency of two accepted infertility factors — one of which may be pill-dependent and the other hardly so — were compared for women who had and had not used oral contraceptives The results must be interpreted as a sign that oral contraception suppresses fertility by the development of oligo- and amenorrhea The chronological relation between discontinuing the Pill and the development of infertility is not stated For most patients however the oral contraception was discontinued because a pregnancy was desired but in several cases this wish did not arise until a varying period had elapsed after the discontinuation However the oral contraceptives may still be a cause of infertility as demonstrated by Vessey *et al* (13) These authors found a decreasing fertility suppressing effect of oral contraceptives over a period of 30–42 months after discontinuation It is not apparent from their publication whether the infertility was due to oral contraception induced oligo-amenorrhea — If a causal relationship did exist between the use of oral contraception and the development of oligo- amenorrhea induced infertility in all the 23 patients in our material who had these bleeding disturbances the remaining patients who had used oral contraception but without developing oligo-amenorrhea (76 – 23 = 53) would be expected to show just the same frequency of tubal occlusion at HSG as patients who had not previously used oral contraception (i e 40 per cent) But instead of 40 per cent of 53 = 22 that might be expected there were only *15* (Table V) This difference is not statistically significant but nevertheless great and it indicates that oral contraception may give rise to infertility problems even though the patient does not develop oligo- or amenorrhea

The distribution of the individual infertility diagnoses in the material accords fairly well with previous findings in similar materials The reason for the small number with exclusively male infertility has been discussed above The surgical results seem to be as satisfactory as in the materials of Swolin (12) and Jessen (5) Of our 52 operated patients 22 or 42 3 per cent (48 9 per cent) achieved intrauterine pregnancies compared with 38 per cent of 52 patients in Jessen s material and 22 per cent of 50 in Swolin s Among patients who underwent bilateral salpingostomy 3 out of 17 = 17 6 per cent conceived compared with 36 per cent of 25 in Jessen s material and 18 2 per cent of 33 in Swolin s The comparability of series undergoing operation for infertility even when stating all definable factors that are likely to affect the result can hardly ever be satisfactory because of the innumerable arbitrary factors in the anatomical pathogenesis of infertility

The individual infertility diagnoses will not be discussed in detail Suffice it to mention that the uterine infertility factors are in agreement with those normally accepted except for the group of uterine retroflexion which is generally not considered a cause of infertility (14) A recent study (15) has shown among 1954 pregnant women a statistically significant difference in the frequency of bleeding and abortion in the first trimester between women with and without retroflexion of the uterus This might indicate a lower fertility in women with retroflexion of the uterus

The number of infertility patients with a multifactorial etiology must be expected to increase when modern diagnostic methods are applied as already discussed Whether a causal relationship does exist between the uterine developmental anomalies diagnosed at HSG and mild bleeding disturbances— such as oligo- and hypomenorrhea — cannot be established for certain in spite of the convincing findings as these findings were accidental and not primarily included in the aim of the study However the theory of such a relationship is supported by another study admittedly using the same methodology Semmens (10) found mild oligomenorrhea in 8 per cent of 25 patients with uterus bicornis unicollis uterus septus uterus subseptus and uterus arcuatus This bleeding disturbance is not further commented in his publication and it does not appear to occur in

patients having other congenital anomalies or in 220 out of 500 pregnant patients with developmental anomalies collected from the literature on uterine developmental anomalies in which the menstrual cycle is described On the other hand menorrhagia and dysmenorrhea are common Only a few of Semmens own patients had presented themselves because of infertility problems so that his material differs from ours in this respect Except for uterus septus all the *other three uterine anomalies in Semmens study* show the same appearances on the HSG (2) Five of the 7 patients in our material with oligo- and/or hypomenorrhea exhibited such uterine cavities In one the HSG appearance suggested a uterus septus or bicornis bicollis and in one a uterus unicornis

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GONORRHEAL INFECTION FOLLOWED BY AN INCREASED FREQUENCY OF CERVICAL CARCINOMA

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Abstract In a town with a fairly centralized health service and a well organized gynecologic health control women who had had gonorrhea in 1954 or 1955 were reviewed for presence of cervical neoplasia and compared with age matched controls Of 164 women studied 29 (17 7 per cent) had 24 or 23 years later developed cancer *in situ* compared [illegible] (4 3 per cent) of the controls ($p < 0\ 001$) while 8 (4 3 per cent) had invasive cancer colli uteri against only one (0 6 per cent) of the controls ($p < 0\ 02$) Malignant disease of the portio proved at least four times as common among the women with gonorrhea in their history as among the controls The findings corroborate the view that cervical carcinoma is a sexually transmitted disease

It may be assumed that at least every fourth woman who had had gonorrhea had been or is a carrier of the carcinogenic agent(s) It is probably easier to search for and detect such agents in association with gonorrhea than in patients with already manifest cancer of the uterine cervix

Sexual intercourse is thought to play an important role in the development of cervical carcinoma The disease is also more common among married women (5) It is rarely diagnosed in nuns (3) Its frequency is increased among women who had their first pregnancy early in life (8) and among women who started their sexual activity while still relatively young (16) Sexual promiscuity (15) prostitution (13) and low socio-economic status (6) are other factors related to an increased frequency of carcinoma of the cervix Further evidence of sexual intercourse being involved in the causation of the disease is the relatively high frequency of vaginal infections in such patients The frequency of cervical carcinoma is reported to be increased in women who have or have had venereal disease (4 9 10 14) In England Scotland and Wales a covariation has been demonstrated for frequency curves of cervical carcinoma and venereal disease in two cohorts 20 years apart (1) The frequency of cervical carcinoma of the cervix is also reported to be high in marital clusters (7) The carcinogenic agent common in these studies is not known Herpes virus (12) might be responsible but so too could be carcinogenic metabolites of bacterial origin

The present study was designed to get an idea as to how to trap the carcinogenic factor and to elucidate the latency period between infection and development of cervical cancer We therefore reviewed women who had had gonorrhea 23 or 24 years previously and been repeatedly examined cytologically since then The occurrence of preinvasive and invasive cervical carcinoma was recorded and compared with the corresponding figures in closely age matched controls

PATIENTS AND METHODS

The material consisted of the records of 164 (42 2 per cent) of 389 women with gonorrhea who had been seen at the Department of Gynecology or Department of Venereal Diseases Malmö General Hospital in 1954–55 and who were still living in the area of Malmö which is served by this hospital only In all of them the diagnosis had been confirmed by culture of material from the uterine cervix urethra and sometimes from the rectum From 1956 they had been followed cytologically either by gynecologic practitioners or at the Department of Gynecology at the same hospital From 1966 they had taken part in mass screening examinations every fourth year When the vaginal smears showed changes biopsy specimens had been obtained by means of the colposcope The diagnosis of carcinoma of the cervix was always verified by histologic examination of biopsy specimens or of specimens obtained at conization or hysterectomy

The controls consisted of 164 closely age matched women who had been examined with cytological smear technique in the same way as the patients with gonorrhea in their history The frequency of gonorrhea in the control group was calculated to be 0 5–1 0 case according to the statistics for venereal disease in Malmö

Fisher s exact test was used in the statistical analysis

Table I *Preinvasive and invasive cervical carcinoma in women who had had gonorrhea 24 or 23 years previously (n = 164) compared with controls (n = 164)*

Stage	Patients	Controls
Ca in situ	29 (17 7)	7 (4 3)
Invasive ca colli uteri	8 (4 9)	1 (0 6)
Total	37 (22 6)	8 (4 9)

Figures within parentheses denote per cent

RESULTS

Carcinoma *in situ* had developed in 29 (17 7 per cent) of the 164 women who had previously had gonorrhea compared with 7 (4 3 per cent) of the controls ($p < 0\ 001$) Invasive cervical carcinoma was diagnosed in 8 (4 9 per cent) of the patients against one (0 6 per cent) of the controls ($p < 0\ 02$) Preinvasive or invasive carcinoma was thus demonstrated in 37 (22 6 per cent) of the patients but in only 8 (4 9 per cent) of the controls (Table I) which implies a relative risk of 4 6 ($p < 0\ 001$) All the invasive tumors of the cervix were squamous epithelial lesions No adenocarcinomas were seen

The age distribution of the patients at the time of infection with gonorrhea and at the time of diagnosis of carcinoma is given in Table II The frequency of gonorrhea was highest in the 21 – 25 age class The youngest patient was 15 years old at the time of the diagnosis and the oldest 46 The ages of the patients with carcinoma *in situ* ranged from 26 to 60 years (mean 35) at the time of the diagnosis The corresponding figures for the controls were 29 to 56 (mean 37) Invasive cervical carcinoma was diagnosed in patients between 35 and 60 years (mean 44) The only control who had this advanced stage was 41 years at the time of diagnosis Of the 8 patients with invasive cervical carcinoma one was in stage 1a 5 in stage 1b one in stage 2b and one in stage 4 In the control group the single case of invasive carcinoma was in stage 1b

Fig 1 shows the interval between the time of infection with gonorrhea and the diagnosis of carcinom *in situ* or invasive cervical carcinoma The mean for carcinoma *in situ* was 11 6 years and for invasive carcinoma 13 5 years One 51 year-old patier in whom a Papanicolaou smear suggested further investigation was not seen again until she was 60 was then found to have invasive cervical carcinoma in stage 2b

Fig 2 shows the intervals between the diagnosis of gonorrhea and of carcinoma *in situ* or invasive cinoma regardless of age of the patients shortest interval for carcinoma *in situ* and for invasive cervical carcinoma was 6 years the longest 21 and 23 years respectively The curve shows substantial increase after 11 years After additional years the frequency of new cases of carcinoma *in si* decreased while that of invasive carcinoma did not

Of the remaining 127 women with previous gonorrhea examined but not registered as having cervical neoplasia there were 5 in whom vaginal smears shown a Papanicolaou score of IV – V and not be persuaded to undergo further investigation. Twenty seven women had shown changes which only temporary however or which further investigation had shown to be benign The figures for the control group were 2 and 15 women.

DISCUSSION

The investigation corroborated the finding in earlier retrospective investigations that cervical more common among women with vaginal in their history The present study can be considered as a prospective investigation of a well defined clinical material of patients with gonorrheal infection diagnosed at Malmö General Hospital in 1954 and 1955 by culture of material from the cervix urethra and sometimes also from the rectum When starting

Table II *Age of patients at diagnosis of gonorrhea and of patients and controls at diagnosis of cervical neoplasia*

Age groups	≤ 15	16 – 20	21 – 25	26 – 30	31 – 35	36 – 40	41 – 45	46 – 50	51 – 55	56 – 60	Total
Gonorrhea infection	1	45	66	26	8	8	7	3			164
Ca in situ				10 (2)	9 (2)	5 (1)	2 (1)	2		1 (1)	29 (
Invasive ca colli uteri					2	1	2 (1)	2		1	8 (

Figures within parentheses denote controls

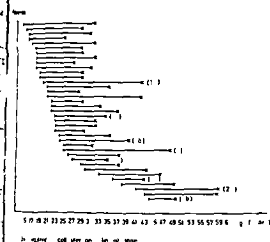


Fig 1 Interval between diagnosis of gonorrhea and carcinoma *in situ* or invasive cervical carcinoma

retrospectively with women in various stages of cervical carcinoma anamnestic data about venereal disease are of doubtful value and are often denied by the patients

Of the primary material of 389 patients 164 (42 2 per cent) were still alive and residing in the catchment area of the hospital in 1978 when they were reviewed for preinvasive or invasive cervical carcinoma There is no evidence of any significant difference in general health between the women still living in Malmö and the remainder who had moved from the catchment area and were therefore not included in the material It is possible however that the gynecologic screening of as many as 91 8 per cent of all women up to 69 years of age in Malmö (2) might have resulted in a higher frequency of early diagnosis of cervical carcinoma than elsewhere This possibility is strengthened by the coincidence of the rise of the curve in Fig 2 in the 11th year after infection with gonorrhea simultaneous with the inception of the screening project

The controls consisted of closely age matched women who had participated in the screening in exactly the same way as the women known to have previously had gonorrhea Since we were unaware whether the 164 controls had previously had gonorrhea or not they may be regarded as a representative sample of the general female population of the town with an anticipated negligible incidence of 0 5 – 1 0 case in this group

As long as we do not know the causal factor of carcinoma *in situ* or of invasive cervical carcinoma we prefer to use the term interval instead of latency period for the time between the diagnosis of gonorrhea and the diagnosis of malignant changes in the portio

We cannot say anything about the actual causal agent of the malignant process i e whether it could be *Neisseria gonorrhoeae* alone or *N gonorrhoeae* combined with some other simultaneously acquired infectious agent of bacterial or viral origin (11) Furthermore a carcinogenic factor acquired at the same time as the gonorrheal infection cannot be excluded

Assuming that the causal agent that started the malignant process was acquired in association with the gonorrhea the youngest group is the most interesting In view of their age they could hardly have been exposed to cancerogenic agents for any length of time before they had been infected with *N gonorrhoeae* This would mean that in this age class the interval (12 4 years) between the diagnosis of gonorrhea and the detection of carcinoma *in situ* or invasive carcinoma might be a fair estimate of the latency of such lesions

The arithmetic mean interval between gonorrhea and carcinoma *in situ* was 12 4 years in the 15 – 20 years group compared with 11 in the remaining patients i e a difference of only 1 4 years This difference might be explained by genetic lability with increasing age or previous unknown infections Women who acquired the infection later in life might have been exposed to some causal agent of the malignant process earlier in life If so it would explain the

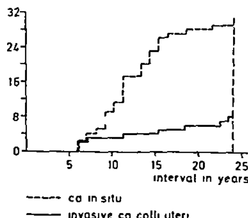


Fig 2 Interval between diagnosis of gonorrhea and carcinoma *in situ* or invasive cervical carcinoma irrespective of age

shortness of the ınterval between the dıagnosıs of gonorrhea and of preınvasıve or ınvasıve carcınoma of the cervıx ın such women Furthermore one can not exclude the possıbılıty of their havıng had gonor rhea even on some still earlier occasıon

It was not thought worthwhile to study the effect ıf any of parıty or socıo economıc status as such an ınvestıgatıon would have been very laborıous and the results would hardly have warranted any clear-cut conclusıon for two reasons first substantıal changes ın socıo economıc status durıng the long perıod covered by the present study and second the ıncreas ıng frequency of cohabıtatıon We do not belıeve that prostıtutes were over represented ın our materıal but rather that ıt ıs an acceptable sample of urban women wıth gonorrhea ın their hıstory

Herpes genıtalıs and/or other genıtal ınfectıons whıch may occur alone or combıned wıth gonorrhea may be of ımportance ın the development of malıg nant lesıons Vagınal smears from a group of 37 women ın our hospıtal who had *1 – 5* years earlıer had vırologıcally verıfıed *herpes genıtalıs* wıthout coex ıstıng gonorrhea were examıned for cervıcal neo plasıa Cytologıcally 35 of the women had a Papanıcolaou smear I and 2 a Papanıcolaou smear II In both cases bıopsy showed benıgn atypıa (17) Thıs does not mean that herpes ıs of no noteworthy ımpor tance but the shortness of the ınterval precludes any defınıte conclusıon as well as any comparıson wıth women who had prevıously had gonorrhea

The present results clearly show that the rısk of developıng malıgnant lesıons ın the portıo was four tımes as hıgh ın women who had had gonorrhea as ın those who had not Thıs ıncreased rısk ıs suffıcıent to warrant partıcular attentıon at the gynecologıc ex amınatıon of such women

The sımılarıty ın age dıstrıbutıon regardıng the oc currence of cervıcal neoplasıa between patıents and controls suggests that gonorrhea ıs assocıated wıth a carcınogenıc agent but less lıkely wıth a promoter agent

In search for the carcınogenıc agent of carcınoma of the uterıne cervıx one mıght expect a better chance of fındıng thıs agent at the tıme of ınfectıon than when a carcınoma of the uterıne cervıx has already reached a preınvasıve or ınvasıve stage

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SEROUS PAPILLARY NEOPLASMS ARISING IN PARAMESONEPHRIC PAROVARIAN CYSTS

A report of eight cases

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bstract Eight cases of papillary serous cystadenoma aris ng in paramesonephric parovarian cysts are presented None of these benign lesions were diagnosed preoperatively as such and were only detected pathologically In only one case was the tumor bearing cyst symptomatic owing to its large size The etiology pathogenesis and evolution of this lesion are briefly discussed

Parovarian cysts of paramesonephric origin are very common but rarely give rise to clinical complications One of the rarest complications of these cysts is the econdary development of an intracystic papillary tu nor benign or malignant (8) These tumors are so are that with one exception (4) they have been doc mented as individual case reports (5 7) So far only ne carcinoma arising within a paramesonephric cyst f the parovarium is on record (1) while there is one eport of a carcinoma originating from parovarian nesonephric rests (9)

Secondary neoplasia developing within parameso ephric parovarian cysts has not been investigated ystematically This report documents a systematic tudy of all parovarian cysts removed surgically or ubmitted along with excised adnexae Over a three ear period eight papillary tumors arising in para nesonephric parovarian cysts were seen

MATERIAL AND METHODS

The study material obtained from women ranging in age from early twenties to late seventies was heavily biassed in favor of young women aged twenty to forty It consisted of 1 9 4 pairs of fimbriated distal tubal segments removed for sterilization and of 308 uteri bearing one or two attached tubes Eleven parovarian cysts were submitted separately

All distal tubal segments removed for tubal sterilization and all tubes along with excised uteri were carefully scruti nized for visible paratubal (parovarian) cysts Their location (8) was identified as fimbrial (corresponding to the hydatid cyst of Morgagni) infratubal or inferior (lying within the concavity of the distal ampulla) supratubal or superior (ly ing subserosally on the rounded superior aspect of the tube) Their number size shape color consistency were noted They were then opened and their inner walls were carefully inspected for opaque areas or foci of visible intracystic papillary ingrowths The cysts were abundantly sampled for histology and all areas of thickening or intracystic papillary growth were processed in toto The parovarian cysts sepa rately submitted were studied in the same way and approp riate samples taken The paraffin-embedded sections were stained with hematoxylin and eosin and the special stains used on selected cases included the Masson Trichrome for the differentiation of smooth muscle and fibrous tissue the PAS/PAS-Diastase combination for glycogen and the PAS-Alcian Blue stain for the detection of neutral and acid mucopolysaccharides and the delineation of basement mem brane

RESULTS

Parovarian cysts were identified in nearly 92 per cent of the cases studied and the infratubal variety was by far the commonest with the fimbrial cyst being a poor second These round or ovoid cysts ranging in size from 1 mm to 12 cm were lined by a smooth thin translucent wall traversed by many stretched blood vessels In eight cases (Table I) the typically smooth inner lining was variably coated by single or multiple closely packed clusters of firm greyish white ver rucous ingrowths (Fig 1) These clusters ranging in size from 2 mm to 3 7 cm and in height from 1 mm to 1 8 cm were easily detected on the inner cyst lining and when large enough could also be palpated on the outside as focal thickenings of the wall

Histologically the diagnosis of papillary serous cystadenoma (Figs 2 and 3) was based on the pres ence of closely packed predominantly fibrous or edematous papillary ingrowths lined by low cuboidal tubal epithelium continuous with a similar epithelium

Table I

Patient	Age (years)	Clinical data	Relevant pathological findings
1	33	Elective tubal sterilization by distal salpingectomy	Fimbria and ampulla of right tube arched over infratubal intraligamentous cyst measuring 6×4×5 cms Tense cyst filled with clear fluid lined by 1–2 mm thick translucent wall with few clustered tiny shallow endophytic growths *Histology* Papillary serous cystadenoma arising in paramesonephric cyst
2	29	Postpartum tubal sterilization by distal salpingectomy	Two cysts in mesosalpinx. Larger infratubal para ampullary cyst measuring 6 mms across filled with thick jelly like pale yellow fluid lined by 1 mm thick translucent wall with small focus of opacity but no definite papillae *Histology* Microfocal papillary serous cystadenoma in paramesonephric cyst
3	28	Cesarean section for cervical dystocia Tubal sterilization by distal salpingectomy	Two intraligamentous infratubal paraampullary cysts Larger cyst measuring 15 mms across filled with clear fluid lined by smooth 1 mm thick translucent wall with tiny clusters of grape like sessile papillary ingrowths *Histology* Papillary serous cystadenoma in paramesonephric cyst.
4	33	Elective tubal sterilization by distal salpingectomy	a) Thick walled opaque infratubal intraligamentous cyst measuring 15×12×6 mms and lying inferior to ampulla of right tube Lined by smooth wall with many clustered finely granular verrucous ingrowths *Histology* Papillary serous cystadenoma in paramesonephric cyst b) On left side similar opaque cyst measuring 3 cms in diameter and showing extensive fine granularity of inner wall. *Histology* Papillary serous cystadenoma in paramesonephric cyst
5	41	Elective tubal sterilization by distal salpingectomy Pelvic floor repair for prolapse	Left fimbrial cyst measuring 5 mms across filled with clear fluid lined by 1 mm thick translucent wall with few finely granular ingrowths *Histology* Papillary serous cystadenoma in paramesonephric cyst.
6	4	Ruptured left ectopic pregnancy left salpingectomy	Infratubal parovarian cyst 1 cm across and containing inspissated jelly like yellowish green material with few barely visible ingrowths *Histology* Early papillary serous cystadenoma in paramesonephric cyst
7	41	Elective tubal sterilization removal of distal right tube with attached cyst excision of segment of left tube (Pomeroy technique)	Infratubal parovarian cyst measuring 3 5 cms and containing clear slightly viscous fluid Single cluster of firm greyish papillary ingrowths *Histology* Papillary serous cystadenoma in paramesonephric cyst.
8	31	Lower abdominal and pelvic pain for four weeks Clinical diagnosis o arian cyst Operative findings large right parovarian cyst impacted in pelvis enlarged edematous cystic right ovary separate from cyst left ovarian cyst	a) Right parovarian cyst measuring 12 cms across and weighing 500 grams closely applied to stretched tube Cyst made up of two widely communicating locules filled with clear fluid lined by smooth translucent wall with two small foci of fine verrucous endophytic growths *Histology* Papillary serous cystadenoma in paramesonephric cyst. b) Right ovary enlarged with marked edema and follicular cysts c) Left ovarian cyst intracystic papillary serous cystadenoma

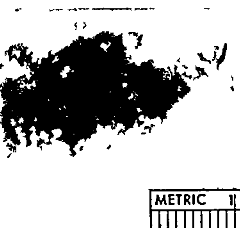
covering the flat surface of the cyst wall The serous nature of the cyst was established by its histologic and tinctorial similarities to tubal epithelium i e the presence of scanty glycogen and variable amounts of adluminal neutral and acid mucopolysaccharides The cyst was identified as paramesonephric and par ovarian by its epithelium which was tubal histolog ically and tinctorially (Fig 4) by the lack of smooth muscle and ovarian tissue in its fibrous wall and by the absence of thin shallow intracystic tubal fronds typically seen in accessory tubes or ostia

Case 8 was exceptional in being clinically symptomatic by virtue of its size Pathologically the cyst dif fered from the others only by its unusally large size (diameter = 12 cm and weight = 500 g)

DISCUSSION

These cases fulfil the criteria of papillary cyst adenoma arising within paramesonephric parovarian cysts and closely resemble the previously reported cases (5 7 8) These tumors though similar to their more common ovarian counterparts are fairly char acteristic in showing only patchy involvement of the inner cyst wall (usually less than 20 per cent of its sur face area) and a tendency to close packing of swollen bulbous papillae lined by low cuboidal tubal epithelium and subtended by edematous or fibrous hypovascular cores

Three possible sites of origin for this lesion deserve consideration The most likely site of origin is clearly the pre existing parovarian cyst which is develop-



1 Gross photograph of firm velvety closely packed ver
ous ingrowths typical of papillary serous cystadenoma
ing in parovarian cyst Note translucent wall with stret
d blood vessels



Fig 3 Closely packed bulky edematous and fibrous papillae lined by low cuboidal epithelium (H & E × 80)

ital in origin and is frequently seen at all ages (8) s suggestion is supported by the strict localization these intracystic tumors near the tubal ostium re developmental paramesonephric cysts are pre and also by the identity of these tumor bearing s and their non neoplastic counterparts The se d site an endosalpingiotic cyst (2) arising within accessory or super numerary ovary is not supted by the consistent absence of ovarian tissue in cyst wall A third possibility (5 7) i e origin n an endosalpingiotic focus in the parovarium we consider unlikely since the strict confinement of these tumors to the parafimbrial and para ampullary tissues does not correspond to the widespread distribution of endosalpingiosis from the tubal ostium to the cul-de sac (6)

Our systematic study which only uncovered eight cases of this tumor in a series exceeding 2 200 cases confirms the rarity of this secondary complication of these parovarian cysts and does not justify their routine en passant removal during pelvic surgery However since there is a tendency for these lesions to occur in larger cysts and since their full neoplastic potential is still unknown it might be wise to remove



2 Parovarian cyst with focal papillary cystadenoma ort arrow) and fibrous wall Note adjoining tubal fim a (long arrow) (Masson Trichrome × 52)



Fig 4 Flat non neoplastic lining of parovarian cyst showing features of tubal epithelium i e occasional clear ciliated cells (arrow) and abundant secretory cells with adluminal deposits of mixed neutral and acid mucopolysaccharides (PAS-Alcian Blue × 890)

the large asymptomatic ones especially as they can unpredictably expand and cause clinical problems

The etiology and pathogenesis of secondary neo plasia arising in parovarian cysts remain unknown and careful review of the clinical data of our small series of patients has yielded no meaningful informa tion Bilaterality concurrence with a similar intra ovarian cystadenoma and a predilection for occur rence in the most common infratubal intraligament ous cyst have been noted but the series is too small for significant deductions The predominantly small size of these secondary tumor foci within these parovarian cysts their inactive looking low cuboidal epithelium and the fibrous or fibrocalcific regression of their bulky cores suggest that these tumors tend towards spontaneous regression rather than progression to malignancy which appears to be exceptional (1) It is noteworthy that the eight documented cases of ovar ian cancer exhibiting spontaneous regression have been papillary serous cystadenocarcinomas (3)

These tumor bearing cysts are clinically indisting uishable from their non neoplastic counterparts and when symptomatic the signs and symptoms are due entirely to cyst size The intracystic tumor cannot therefore be diagnosed preoperatively but at opera tion its presence can be suspected if the typically thin translucent cyst wall shows focal or patchy opacity and thickening It is hoped that this report will stimu late interest in this lesion and allow the collection of enough data for meaningful analysis

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PROBABLY VIRUS-INDUCED EPITHELIAL LESIONS IN PREINVASIVE CERVICAL CANCER

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Abstract There is an urgent need to approach the evaluation and classification of cervical intraepithelial lesions and their cytopathological correlations as specifically as possible Preinvasive cancer (differentiated and undifferentiated carcinoma in situ) of the uterine cervix the most advanced stages of cervical intraepithelial neoplasia should be clearly defined and described and the diagnostic and therapeutic management including the follow up of the patients outlined in detail

The present results based on a material of 524 cone biopsies clearly indicate the existence of two different types of probably virus-induced epithelial lesions in the two histopathologic groups of preinvasive cancer of uterine cervix

Cervical neoplasia probably develops as a result of a combination of initiating events and promoting agents Virus infections sexually transmitted from male to female and inducing epithelial lesions might be such an initiating event and even a promoting agent

Rawls *et al* (12) discuss the role of virus infection in the etiology of cervical neoplasia and stress that a virus might act as a carcinogen or co-carcinogen or that a virus infection may follow a neoplastic transformation which indicates a greater affinity of cancerous tissue for the virus Meisels *et al* (6) found a surprisingly high occurrence of condylomatous lesions a venerally transmitted viral infection which at times had been interpreted as dysplasia of the uterine cervix In view of the fact that condylomata acuminata have been proved to undergo malignant transformation and that they behave epidemiologically in a way similar to carcinoma of the cervix the authors speculate that these viral infections might represent a precursor of cervical neoplasia They state that condylomatous viral lesions are generally present in a younger group than dysplasia and carcinoma in situ (CIS) Both condylomata and cervical neoplasia are directly related to sexual promiscuity and an early onset of sexual activity It is conceivable that the immature cervix when still covered by a fragile single layer of epithelial cells could be more vulnarable than the mature cervix

Naib *et al* (8 9 10) discuss the relation of cyto- and histopathology of genital herpes virus infection to cervical neoplasia The authors analysed 673 cytologically detected cases of herpes genitalis with regard to the association of histologically confirmed cervical neoplasia Among these 673 cases there were 69 women with dysplasia 25 with CIS and 11 with invasive cervical cancer a total of 105 cases (15 6 per cent) of neoplastic and malignant epithelial changes in the uterine cervix The authors reported data from serological studies which indicate that the herpetic infections were not newly acquired but instead represented recurrences of latent herpes the initial event probably having occurred months or even years prior to the detection of the cervical neoplasia The age prevalence of genital herpes was found to be 5 years earlier in the study group than that of cervical dysplasia and 10 to 15 years earlier than that of CIS

Tobin *et al* (15) described an animal model that demonstrates the development of varying degrees of basal cell hyperplasia metaplasia and dysplasia following herpes virus infection Although the study spanned a period equivalent of 60 human years there was no evidence of anaplasia The authors discuss the role of herpes virus as an initiator in the process which leads to cervical carcinoma

As important as studies on the relation of genital virus infection to cervical neoplasia is the evaluation of the occurrence of histopathologically confirmed probably virus induced epithelial lesions close to or within foci exhibiting dysplasia or CIS (14) and their early detection by means of cervico-vaginal smears According to Naib *et al* (10) hypertrophy of the cytoplasm and nucleus of infected cells is usually observed in viral infections The cells increase in size and show nuclear and cytplasmic edema as indicated by the frequent appearance of perinuclear halo



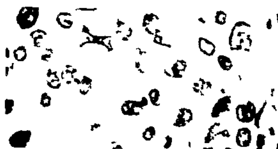


Fig 1 and 2 A probably virus induced epithelial (Type I) lesion is located between normally differentiated squamous epithelium (to the right) and neoplastic epithelium (to the left) The lesion shows hypertrophy of the cytoplasm and nucleus with perinuclear halo and in many cells the nuc chromatin is displaced to the periphery (×175 and × respectively)

These are a result of the shrinkage of the enlarged nucleus and cytoplasm due to dehydration of the cell during fixation and staining The nucleoli also enlarge and become vacuolated The nuclear chromatin is displaced to the perifery and results in central nuclear clearing Multinucleation is also seen Granules appear in the centre of the nucleus and form an intranuclear inclusion surrounding by a more or less prominant halo Cells infected by virus exfoliate idly and usually appear abundant in cervical smears when they show degenerative changes in the cytoplasm and nuclei with vacuolization ballooning and bizarre shapes

MATERIAL AND METHODS

In the present study 524 cervical cone biopsies 421 with preinvasive cancer (differentiated and undifferentiated CIS and 103 with dysplasia in women 16–39 years of age were evaluated histologically as well as cytologically in order to investigate the occurrence of probably virus induced epithelial lesions

The cones were fixed in formalin dehydrated in paraffin For investigate purposes 10 to 15 serial sections were embedded in paraffin blocks sectioned and stained by the hematoxylin eosin and van Gieson techniques

The cytological smear 3 to 7 specimens from each case investigated were collected from the cervix and vagina fixed and stained according to the original Papanicolaou technique (11) The histological as well as the cytological material was handled by the staff of the University Hospital Uppsala during 1970–79





Fig 3 and 4 An area of probably virus induced epithelial (Type II) lesion is located within preinvasive cancer contrasting with the neoplastic squamous epithelium of small and dark undifferentiated cells Note hypertrophy of the cytoplasm and nucleus edema and perinuclear halos The nuclei are dense and the nuclear chromatin displaced to the periphery (×175 and ×640 respectively)

RESULTS

In differentiated preinvasive cancer the normal stratified structure of squamous epithelium is no longer recognizable The basal cell layers consist of undifferentiated neoplastic cells with small and dark uniform nuclei and indistinct cell borders The middle and especially the upper cell layers show larger neoplastic cells and the degree of differentiation may vary from incipient to moderate while the cell borders are distinct In all cell layers there is considerable variation in the size and shape of the cells and the nucleo-cytoplasmic ratio is significantly increased to within malignant limits Mitoses and nuclear pleomorphism are usually found throughout the lesion

In *undifferentiated CIS dark undifferentiated cells* with indistinct cell borders are found throughout the lesion The nuceli are crowded and vary in size and shape Areas with bizarre nuclear enlargement create a highly malignant pattern of the lesion and typical and atypical mitoses are often seen in the superficial cell layers

The cellular pattern of differentiated CIS shows incipient or distinct differentiation The nucleo-cytoplasmic ratio is greatly increased There is considerable variation in the nuclear size and shape and the hyperchromatic and irregular nuclei are coarse granular or filamentous in their chromatin pattern Bizarre differentiated neoplastic cells are frequent Some of the squamous cells show only incipient differentiation with no differentiation of the basal cell layers

The cells of undifferentiated CIS are small and dark with scanty cytoplasm and a greatly increased nucleo-cytoplasmic ratio The cytoplasmic borders are indistinct The nuclei are prominent and show pleomorphism aniso nucleosis and hyperchromasia with coarse clumping of the chromatin The nuclear borders are irregular and the nucleoli vary in number size and shape

In dysplasia the basal cell layers consist of small and dark undifferentiated neoplastic cells similar to those of undifferentiated or differentiated CIS The cells of the lower middle layers consist of larger cells showing incipient differentiation and dark nuclei and the upper middle cell layers exhibit fairly well differentiated squamous cells which are larger and fewer towards the surface The nucleo-cytoplasmic ratio is significantly lower in the middle cell layers than in the basal cells and pleomorphism in nuclei as well as mitoses are significantly less frequent The superficial cells are well differentiated normal or only slightly atypical flattened squamous cells

In the present material 421 cone biopsies were evaluated with respect to the occurrence of histologically confirmed probably virus induced epithelial lesions close to but unconnected with preinvasive cancer or within preinvasive cancer Two basic patterns were found

Areas of probably virus induced epithelial lesions were found to be located close to but without any connection with squamous epithelium exhibiting preinvasive cancer (Type I) These well demarcated areas showed hypertrophy of the cytoplasm and nucleus and larger cells with nuclear and cytoplasmic edema Because of the dehydration of the cell during fixation *and staining a perinuclear halo is observed and the* nuclear chromatin is displaced to the periphery Multinucleation and intranuclear inclusions are also seen in these epithelial areas As a rule there is a sharp border between the deep denser cell layers and the superficial layers consisting of clear cells with degenerating nuclei surrounded by a clear halo that may occupy most of the cell (Fig 1 – 2)

Areas of probably virus induced epithelial lesions located within preinvasive cancer as sharply demarcated light areas of squamous epithelium are considered to belong to a special group of these changes (Type II) These sharply demarcated foci contrast with the neoplastic squamous epithelium which consists of small and dark undifferentiated cells or cells exhibiting incipient or moderate squamous differentiation (Fig 3 – 4)

Table I shows that in 51 out of 421 investigated cases (12 1 per cent) a probably virus induced and morphologically clearly recognizable and definable lesion was found in 26 (6 2 per cent) without any connection to preinvasive neoplasia In 25 cases (5 9 per cent) probably virus induced lesions were within areas of preinvasive carcinoma Thus the total number of probably virus induced lesions within preinvasive carcinoma seems to be about the same as in those lesions not connected with CIS

The cytopathologic pattern of preinvasive cancer was investigated in the present study by evaluating the occurrence of benign cells (normally differentiated squamous cells metaplasia inflammatory changes) dysplastic (dyskaryotic) squamous cells and malignant cells exhibiting squamous differentiation of high moderate or low degree In all a series of cervico-vaginal smears from 128 women with preinvasive cancer was investigated and correlated w

Table I *Incidence of probably virus induced lesions in 421 cones with preinvasive cervical cancer*

	CIS Number of cones		
	Differentiated	Undifferentiated	Total
Viral lesion Type I	10 (8 7)	16 (5 2)	26 (6 2)
Viral lesion Type II	17 (14 8)	8 (2 6)	25 (5 9)
CIS only	88 (76 5)	282 (92 2)	370 (87 9)
Total	115	306	421

the figures within parentheses denote number in per cent

series of dysplasia in 103 women in the same groups The results are shown in Table II

Table II shows that the screening results in cases of preinvasive cancer were good there were only 3 cases of false negative results (2 per cent) The results in cases of dysplasia were significantly different with 8 per cent (9 cases) false negative and 49 cases (48±5 per cent) classified as CIS A significant number (see Discussion) of these inaccurate results was induced by a false interpretation of probably virus induced lesions

DISCUSSION

In the early detection of cervical neoplasia there is a tendency to classify an increasing number of cases exhibiting more or less total replacement of squamous epithelium by atypical but not necessarily neoplastic or malignant cell layers as preinvasive cancer

It is important to recognize the typical and different morphological pattern of probably virus induced lesions in squamous epithelium described in detail by several authors (6 7 8 9 10 15) in histologic sections as well as in cervico vaginal smears

The probably virus induced epithelial lesions are located in the cervical canal either close to but unconnected with areas of preinvasive cancer or within the cervical neoplasia and are seen as well demarcated pale areas exhibiting a typical morphologic pattern

Reviewing smears previously diagnosed as representing patterns of mild dysplasia Meisels *et al* (7) found that 70 per cent of the cases were consistent with condylomatous changes induced by the venerally transmitted virus of condyloma acuminatum The cytologic patterns of these lesions were described in detail by Meisels and Fortin (6) Dyskeratosis condensed and hyperchromatic nuclei perinuclear clearing multinucleation and inclusion bodies are cytologic changes that might be interpreted as corresponding to cervical neoplasia

The progression of premalignant cervical lesions into CIS and invasive cancer is of great importance especially in the younger age groups On the basis of the extensive studies of Barron and Richart (1) and Fidler *et al* (4) it can be concluded that 50 per cent of patients with various forms of untreated dysplasia progress to CIS while 28 per cent remain in the stage in which they were detected 16 per cent progress to a higher stage of dysplasia and only 6 per cent show spontaneous regression Finally an unknown number of cervical premalignant neoplastic lesions probably progress directly to invasive cancer

The pattern of progression and regression of probably virus induced epithelial lesions in the uterine cervix is unknown and should carefully be studied cytologically and histologically in large groups of women The second important question concerning probably virus induced cervical lesions is the therapeutic management of these cases The basic difficulty in answering this question is that these lesions are often found together with classical dysplasia or CIS

In the present study cases with dysplasia could not be included due to the fact that these women as a rule are not investigated and treated by conization following initial cervical biopsies The 103 cases of dysplasia investigated were selected according to age

Table II *Cytopathology of preinvasive cancer (128 cases) and dysplasia (103 cases)*

	Histology	
Cytology	CIS	Dysplasia
Normal differentiation metaplasia inflammation	3 (2)	9 (8)
Dysplasia	24 (19)	45 (44)
Preinvasive cancer	101 (79)	49 (48)
Invasive cancer	–	–
Total	128	103

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and parity (higher than the average woman) and therefore the true frequency of probably virus induced cervical lesion is not known However the cytohistologic pattern can be evaluated and correlated with preinvasive cancer A significant number of the 49 cases (48±5 per cent) cytologically classified as preinvasive cancer was overdiagnosed due to the occurrence of cells or groups of cells in the cervico-vaginal smears exhibiting a typical pattern of viral infection

In 51 out of 421 morphologically investigated cases (12 1 per cent) a probably virus induced epithelial lesion was found the number of lesions within preinvasive carcinoma seems to be about the same as those lesions not connected to CIS

Czernobilsky *et al* (2) discuss the prevalence of inflammatory and proliferative cervical lesions in Jewish and non Jewish women The authors found that in spite of the low incidence of cervical cancer in Jewish patients the prevalence of cervical inflammatory and non malignant proliferative epithelial changes corresponded to the number found in non Jewish populations According to the authors there seems to be two possible explanations for their findings first the histologic spectrum leading to CIS stops at the dysplastic stage or secondly dysplasia may in fact represent a non specific reaction which is not necessarily a stage in the process leading to CIS or invasive cancer of the uterine cervix

Meisels *et al* (5) discuss the role of age at first coitus and the use of oral contraceptives as epidemiological aspects in the development of dysplasia of the uterine cervix The authors conclude that in homogenous populations highly significant correlations were found between the early onset of sexual activity and the occurrence of dysplasia and oral contraceptive use and the occurrence of dysplasia The authors stress that dysplasia behaves epidemiologically essentially as a veneral disease like CIS and invasive cancer and that it remains to be seen whether all dysplasias form one continuum or several different forms exhibiting different rates of progression

Discussing the surprisingly high rate of condylomatous lesions in young women Meisels *et al* (7) speculate that these venerally transmitted viral infections might represent a precursor of cervical neoplasia The possible role of herpes virus as an initiator in the process leading to cervical carcinoma is discussed by several authors (8 9 10 12 15)

One approach is to consider cervical intraepithelial neoplasia a spectrum of one and the same disease beginning from mild dysplasia and ending with undifferentiated CIS According to Richart (13) and Ferenczy (3) there is a logarithmic increase in the number of undifferentiated basal cells with increasing severity of this disease

There is an urgent need to approach the evaluation and classification of cervical intraepithelial lesions and their cytopathologic correlations as specifically as possible Differentiated and undifferentiated preinvasive cancer of the uterine cervix the two most advanced stages of cervical intraepithelial neoplasia should be clearly defined and described and the diagnostic and therapeutic management including the follow up of the patients outlined in detail

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Czernobilsky et al (2) discuss the prevalence of inflammatory and proliferative cervical lesions in Jewish and non Jewish women The authors found that in spite of the low incidence of cervical cancer in Jewish patients the prevalence of cervical inflammatory and non malignant proliferative epithelial changes corresponded to the number found in non Jewish populations According to the authors there seems to be two possible explanations for their findings first the histologic spectrum leading to CIS stops at the dysplastic stage or secondly dysplasia may in fact represent a non specific reaction which is not necessarily a stage in the process leading to CIS or invasive cancer of the uterine cervix

Meisels et al (5) discuss the role of age at first coitus and the use of oral contraceptives as epidemiological aspects in the development of dysplasia of the uterine cervix The authors conclude that in homogenous populations highly significant correlations were found between the early onset of sexual activity and the occurrence of dysplasia and oral contraceptive use and the occurrence of dysplasia The authors stress that dysplasia behaves epidemiologically essentially as a veneral disease like CIS and invasive cancer and that it remains to be seen whether all dysplasias form one continuum or several different forms exhibiting different rates of progression

Discussing the surprisingly high rate of condylomatous lesions in young women Meisels et al (7) speculate that these venerally transmitted viral infections might represent a precursor of cervical neoplasia The possible role of herpes virus as an initiator in the process leading to cervical carcinoma is discussed by several authors (8 9 10 12 15)

One approach is to consider cervical intraepithelial neoplasia a spectrum of one and the same disease beginning from mild dysplasia and ending with undifferentiated CIS According to Richart (13) and Ferenczy (3) there is a logarithmic increase in the number of undifferentiated basal cells with increasing severity of this disease

There is an urgent need to approach the evaluation and classification of cervical intraepithelial lesions and their cytopathologic correlations as specifically as possible Differentiated and undifferentiated preinvasive cancer of the uterine cervix the two most advanced stages of cervical intraepithelial neoplasia should be clearly defined and described and the diagnostic and therapeutic management including the follow up of the patients outlined in detail

The present results based on series of 524 cone biopsies clearly indicate the existence of two different types of probably virus induced epithelial lesions in the two histopathological groups of preinvasive cancer of the uterine cervix

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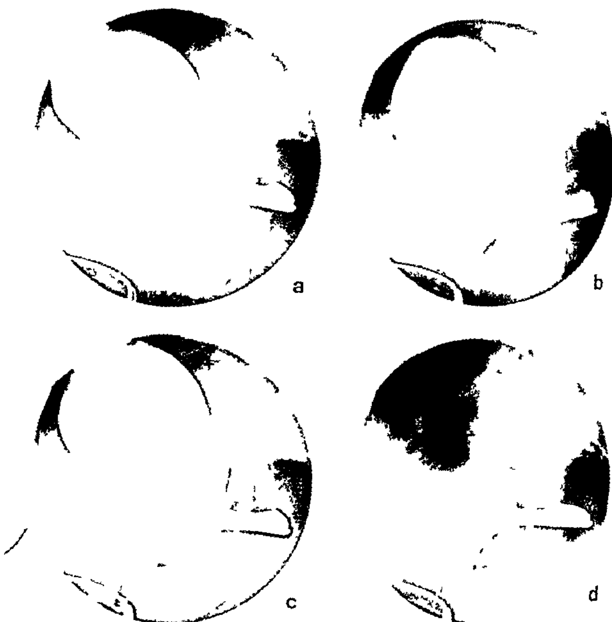


Fig 1 Normal colpo-cysto-urethrography *a* at rest *b* during cough *c* voiding *d* post micturition

One of the groups bladder base incufficiency (b b i) has previously been described by Olesen (9) and in further detail by Olesen & Walter (12) The characteristic morphology is shown in Fig 2 The urethro vesical junction is situated lower and more anterior than normally The resting bladder base thus becomes funnel shaped with absence of the normal flat horizontal area in front of the internal urethral orifice The shape and position of the vagina is normal Clinically this group carries a high incidence of stress incontinence 83 6 per cent Micturition pressures are slightly lower than normal The flows vary from subnormal to high even in the same patient This variability is characteristic while average flow values are normal

Another group presents with a normal resting bladder but during cough the bladder base assumes the same characteristics as described above for b b i (Fig 3) Stress incontinence is a complaint in 82 3 per cent of these cases Forty four per cent showed the same micturition pattern as in b b i during the urodynamic examination while 56 per cent showed either normal or straining micturition

The third group shows more extensive morpholog



Fig 2 Bladder base insufficiency (b b i) *a* at rest *b* during cough *c* voiding *d* post micturition

cal pathology the resting bladder is normal During cough however the entire bladder base slides down in front of the vagina The axis and position of the vagina is normal but the anterior vaginal wall slides down in an anterior direction together with the bladder base presenting an eversion of the anterior vaginal wall in the introitus of the vagina (Fig 4) This we have named a prevaginal or anterior bladder descent (a d) Stress incontinence was present in 80 8 per cent of these patients The urodynamic pattern was different from the preceding groups since 57 per cent used straining resulting in undulating pressure—and flow curves Forty three per cent presented either normal or b b i patterns during micturition

These three groups comprised 198 patients and constituted 47 1 per cent of the total number of investigated patients (The remaining 222 patients presented morphological pictures ranging from normal to severe displacements of bladder and vagina in a postero-inferior direction trigonocele and posterior bladder descent and also included the neurogenic dysfunctions Among these patients 36 5 per cent complained of stress incontinence The urodynamic pattern varied according to the various morhpolog

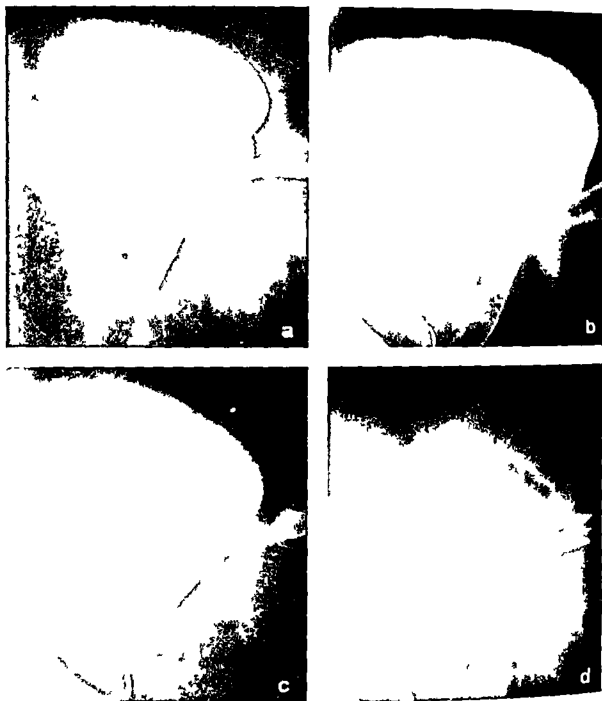


Fig 3 Bladder base insufficiency visible during cough only *a* at rest *b* during cough *c* voiding *d* post micturition

ical and functional disorders They will be dealt with in a separate paper)

In Table I the patients are divided into two groups depending on whether the resting bladder was normal or presented b b i Each of these groups is subdivided according to morphology during cough These four subgroups are further divided according to micturition morphology Three micturition patterns i e normal b b i and a d are represented in each subgroup Four patients could only be classified according to the resting picture and the micturition picture because of unsatisfactory cough radiographs Eighteen patients were not classified because of complicating posterior bladder descent during micturi



Fig 4 Two cases of anterior bladder descent *a* *b* and *c* patient displaying b b i at rest and anterior descent during cough and micturition a₁ b₁ and c₁ patient with normal resting bladder displaying anterior descent during cough and micturition

tion Three patients did not micturate during the examination and one had a urethral stricture

Twenty two patients presented the urodynamic pattern of decreased urethral resistance as described by Palm (13) Eight of these showed normal voiding morphology 7 presented b b i and 7 a d morphology during micturition

Table I *198 patients with anterior bladder suspension defects grouped according to morphology of resting cough and micturition pictures*

ST NG	NOR						NO M L
COUG	b.b.			a.d.			?
M CTU ITIO	NORMAL	b		NO MA	b.b.i.	d	a.d.
NO O T NT	38		9			0	
ST ESS NC %	84	73	89	75	8	80	100

5 CAS COMP ICATE WI POSTE IOR DESC NSUS
2 DI NO M CTU

ESTING	b					
COUG				a.d.		
M CTU ITION	NORMA	b.i.	a.d.	NORMAL	b.b	d
NO OF TI NTS	22	5		3		
ST ESS INC %	77		80	00	00	00

CASES COMPLICATE WITH POSTE IOR DESC NSUS
1 HAD URETHRAL S ICTUR
DID NOT MICTURATE

DISCUSSION

The percentage of women with stress incontinence is very uniform in the various subgroups The morphological differences however are important If the resting bladder is normal and the b b i configuration is provoked only by coughing the patient exhibits the lowest degree of pathology and is labelled grade 1 If the resting picture shows b b i the case is marked grade 2 All cases that show and a d pattern during

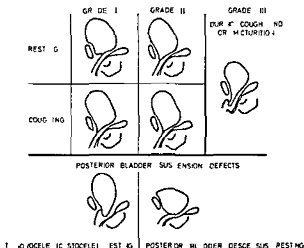


Fig 5 See text for further explanation

cough and/or micturition must have more extensive pathology as the anterior vaginal wall is involved in the displacement The vaginal attachment to the endopelvic fascia must be insufficient It is therefore reasonable to group these cases as showing the severest degree of pathology grade 3 of the anterior bladder suspension defects Fig 5 shows the anterior suspension defects in the three grades as opposed to the posterior bladder suspension defects

This grouping in various grades allows a precise description of underlying pathology and the degree of vement of the supporting tissues Thus it may as an aid in the choice of corrective surgical pro

ption of the low positioned funnel shaped bladder base is widespread in the literature on urinary stress incontinence (1 5 6) Green (4) in a paper on stress incontinence described a type I which corresponds to b b i and a type II which includes a d but also includes all other cases of bladder descent Colpo cysto urethrography by visualization of the vagina enables us to distinguish a d from posterior descent in which the posterior support i e the levator muscles are insufficient and the vagina therefore shows a curved posterior displacement Bethoux *et al* (2) also make this distinction by means of colpo cystograms They find that stress incontinence is typically linked with a normal position of the vagina From our study it cannot be said that stress incontinence is specific to this group Stress incontinence is found in all groups as a fairly common symptom but it is far more typical in anterior bladder suspension defects than in the remaining groups

UNDERLYING PATHOLOGY

The bladder displacement is in anterior and inferior direction Olesen & Grau (10) suggested that the structures which prevent this displacement of the bladder base must be the ligaments in the pelvic fascia i e the arcus tendineus fasciae pelvis which pass in a dorsal direction from the bladder neck to which they are firmly connected

On the basis of these anatomical studies seven patients complaining of stress incontinence and presenting grade 1 and transitional forms between grade 1 and grade 2 have been operated on using a procedure aimed at tightening the arcus tendineus via a suprapubic approach The bladder neck and the fibroelastic nodes on its lateral aspects described by Zacharin (15) were dissected From here the arcus tendineus fasciae pelvis was followed posteriorly for about 5 cm Fig 6 shows the anatomy and the principle of the operation The structures were clearly definable in all instances By tightening the arcus tendineus on each side and approximating the two fibroelastic nodes in front of the bladder neck the normal shoulders of the bladder base were created These shoulders correspond to the flat part of the base in

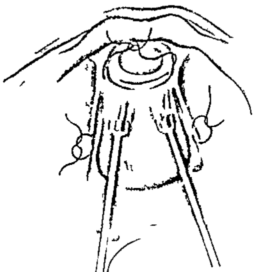
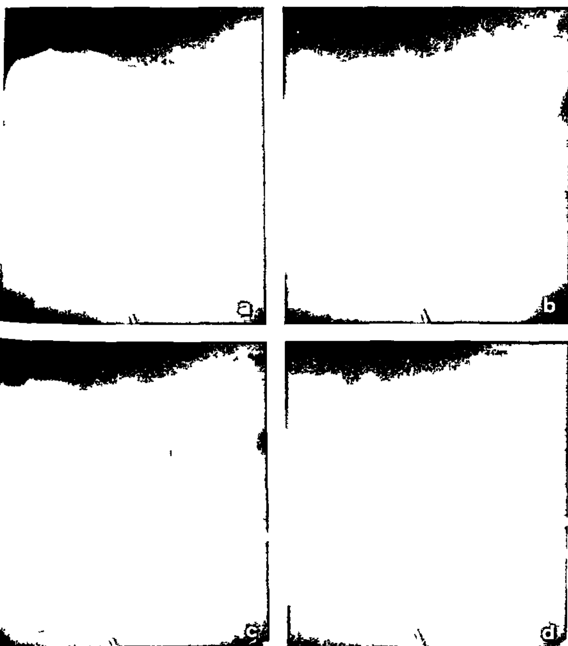


Fig 6 Drawing of operative method Symphysis pubis upwards Bladder retracted displaying in front the bladder neck and the fibroelastic nodes connected to the symphysis by the *pubo vesical ligaments* From the fibroelasti nodes the arcus tendineus fasciae pelvis passes in a postero-lateral direction Tightening sutures are placed in each arcus tendineus and one between the two nodes in front of the bladder neck thus tightening the support around the anterior part of the bladder neck



ig 7 Same patient as Fig 2 after operative tightening of the anterior support of the bladder neck now normalized *a* at rest *b* during cough *c* voiding *d* post micturition

ront of the internal orifice seen on the radiographs The dissection was troublesome and gave con iderable bleeding so the operation is not suitable for outine use

Two patients did not agree to a follow up examina ion In the remaining five patients stress incon inence ceased In one patient symptoms suddenly re appeared after 11 months and follow up examination revealed that the preoperative conditions had recur red Four patients suffered from urgency in varying degrees for about a year after the operation but are now at 18 months nearly symptomfree Follow up examinations (Fig 7) revealed an entirely normal bladder base in a normal position

CONCLUSION

By the use of colpo cysto urethrography uro dynamics dissections and anatomically corrective surgery the existence of a specific group of female bladder suspension defects has been proved The pathology is due to insufficient support of the bladder neck and the anterior part of the bladder base because of laxity of the arcus tendineus fasciae pelvis and/or its firm connection with the bladder neck resulting in a forward downward displacement of the urethro vesical junction A grading from 1 to 3 is established depending on the involvement of the supporting tissue of the bladder neck and of the anterior vaginal wall It is shown how tightening of the arcus tendineus fasciae pelvis results in the establishment of a normal bladder base The bladder base as seen on *the radiographs therefore must* be considered an indicator of the quality of the support of the bladder and not an indicator of a structure in the bladder wall—a base plate—as advocated by Hutch (7)

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POSTERIOR BLADDER SUSPENSION DEFECTS IN THE FEMALE

A radiological classification with urodynamic and clinical evaluation

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Abstract Of 470 female patients examined by means of colpo-cysto-urethrography 51 patients presented posterior bladder suspension defects Two distinct forms were seen 1. Trigonocele (22 patients)—a downward herniation of the trigone between the postero-inferiorly displaced vagina and the bladder neck which is retained in a nearly normal position by muscle fibres from the pubococcygeal muscle and the pubovesical ligaments Symptoms were mostly those associated with prolapse Stress incontinence was rare while urge incontinence cystitis and retention of urine were seen The morphology varied from cases where the herniation disappeared during detrusor contraction (compensated trigonocele) through typical forms to transitional forms between trigonocele and posterior bladder descent

2. Posterior bladder descent (29 patients) comprises postero-inferior displacement of the vagina and bladder base together Two subgroups are discernible A Bladder descent even at rest (16 patients) B Bladder descent only during micturition (13 patients) Symptoms were varied but stress incontinence was found in 31 per cent in group A and 62 per cent in group B Morphological forms varied from two cases that were normalized in position during detrusor contraction (compensated descent) to total prolapse during micturition

Little interest has been focused on the conditions of the female bladder characterized by descent which do not typically cause stress incontinence Hodgkinson & Doub (4) describe two variants the cystocele and the prolapsed bladder as representing various degrees of relaxation of the support of the bladder and urethra not associated with urinary stress incontinence Green (3) has the impression that cystocele and stress incontinence are essentially mutually exclusive Palm (8) on the other hand finds that cystocele and bladder descent are bladder diseases accompanied by stress incontinence One reason for this discrepancy may be that bladder descent consists of two distinct groups Olesen & Walter (7) by visualization of the vagina with contrast medium have shown that bladder descent is made up of two separate entities anterior descent and posterior descent Anterior descent is not caused by a posterior suspension defect but takes place in front of a normally placed vagina It is typically accompanied by stress incontinence This condition will not be further described in this paper Posterior bladder descent on the other hand is caused by insufficient levator support resulting in a postero-inferior displacement of vagina and bladder together This condition has a wide spectrum of symptoms In cystocele the vagina shows the same displacement as in posterior bladder descent but the bladder neck has not followed the vagina in the displacement Instead the trigone has herniated down between the bladder neck and the vagina The present report focuses on these two interrelated conditions constituting posterior bladder suspension defects

For reasons of clarity the term cystocele though commonly used in the literature will be avoided because of the double meaning of the word 1 a bulging anterior vaginal wall demonstrable during a pelvic examination and 2 a herniation of the trigone down behind the bladder neck demonstrable on the radiographs While the former finding is common and not specific for any particular bladder anomaly the latter is specific from a radiological and urodynamic point of view Based on the actual findings and to avoid misunderstandings this radiological and urological cystocele from her on will be termed a trigonocele

METHOD

Colpo-cysto-urethrography i e lateral voiding cysto-urethrography with barium contrast added in the vagina was performed with the patient seated Intravesical pressure was measured transurethrally The flow was recorded by means of a DISA 14F41 uroflowmeter Exposures were guided by the flow curve and were marked electronically on the pressure flow tracings

On a separate occasion the patients were examined clinically gynecologically and urodynamically This includ

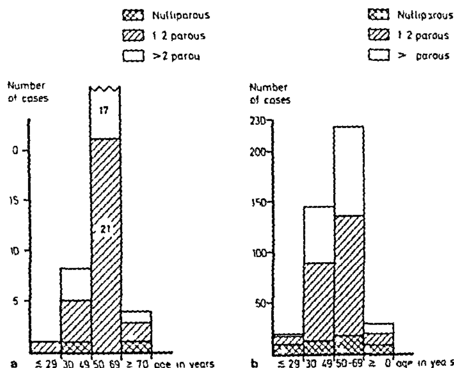


Fig 1 Age and parity bution of posterior sion defect patients *(a)* as posed to whole material *(b)*

water cystometry flow recording and differentiated detrusor pressure measurement

The two examinations were not compared until indepen dent diagnoses had been reached The examination techni que has already been described in detail by Olesen & Walter (7) and Walter *et al* (12)

MATERIAL

r hundred and twenty consecutive examinations were formed and 51 patients displayed posterior bladder suspension defects Age and parity distribution of these pa tients are shown in Fig 1 Vaginal repairs had been perform ed in 16 patients One patient had had both a vaginal repair and an urethropexy Primary urethropexies had been per formed in two patients and five had had a hysterectomy

FINDINGS

Trigonocele Twenty two patients displayed a trigonocele during bladder reservoir function i e on the resting and/or cough radiographs To determine the position of the bladder neck during micturition we measured the urethro pelvic angle (UP) (Fig 2) as described by Olesen & Walter (7) and found that it varied considerably Three patients had very high UP values (above 110) These patients had all been oper ated on with urethropexies Six patients had UP val ues below 70 indicating bladder descent Only one of these patients retained the trigonocele configura tion during micturition while five micturated with the configuration of posterior bladder descent clearly demonstrating the near relationship between the two types of posterior suspension defects

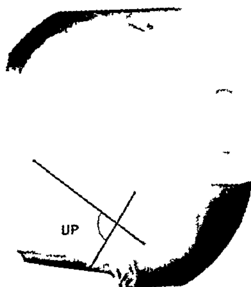


Fig 2 Urethro pelvic angle (UP) The angle between urethra and a line along the posterior surfa e of the symphysis through the lowermost part of the obturator f closest to the picture

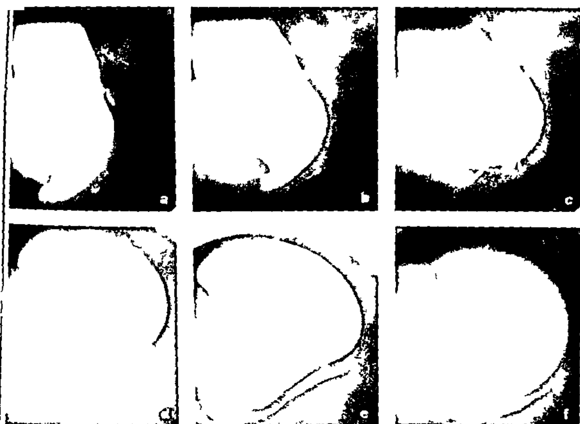


Fig 3 Trigonocele *a* at rest *b* during contraction of the pelvic floor *c* during micturition of patient who compensates the trigonal herniation during detrusor contraction *d* during cough *e* during contraction of the pelvic floor and *f* during micturition of a patient who displays a borderline case on posterior descent during micturition

patients elevated the herniated trigone to an entirely normal position and form during detrusor contraction i e their trigonocele was compensated One patient had a large vaginal cyst distorting the anatomy and one could not micturate during the examination Thus only eleven patients micturated with the typical trigonocele configuration and one of these had a low bladder position They all showed radiological signs of detrusor activity The internal urethral orifice opened only slightly because of the unstraightened trigone (Fig 3)

Urodynamically they all showed detrusor micturition with elevated intravesical pressure Flow curves were low and flat The urethral resistance (intravesical pressure/flow²) therefore was higher than normal varying from 0 2 to 4 0 median 0 7 Frimodt Møller (2) gives normal values for the urethral resistance in females between 20 and 30 years 0 19±0 16 Walter *et al* (13) found normal values in females between 40 and 70 years to be 0 15±0 11 The overall urodynamic picture (Fig 4) corresponds to that of the prostatically obstructed male indicating that the obstruction is near the bladder neck

Two patients showed signs of detrusor overactivity in the cystometrograms Clinically the patients all presented with bulging anterior vaginal walls The symptoms were gynecological complaints 10 straining on micturition 3 retention and cystitis 3 urge incontinence 3 and stress incontinence 3 two of these were due to recurrence after urethropexies i e iatrogenic trigonoceles

Posterior bladder descent Sixteen patients had low lying bladders even on resting radiographs i e the bladder neck was located below the inferior part of the symphysis The vagina showed a central bulge and a displacement in the postero-inferior direction (Fig 5) Thirteen patients had normally positioned bladders during rest but showed descent during micturition to UP values below 70 One patient did not void during the examination Two patients lifted ι

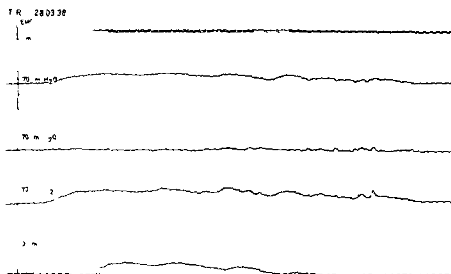


Fig 4 Trigonocele Urodyna mic examination pressure (DP) is calula electronically by abdominal pressure from total intravesical sure (IVP)

bladder base to a normal position during micturition i e compensated descent Micturition morphology for the remaining 26 patients were all of the same type but varied in degree of descent from UP values just below 70° through the typical tea pot form to total prolapse of the bladder with the posterior urethra running directly upwards to a sharp bend at the site of the external sphincter This bend was in all cases the narrowest part of the urethra while the internal orifice was well open

Urodynamically the pattern was varied and independent of whether the resting bladder was low in Eleven patients showed the classical descent with undulating flow and pressure tracings (Fig 6) as described by Palm (8) Pressure was almost entirely abdominal and the urethral resistance varied from 0 1 to 4 0 with a median of 0 6 Six patients voided with a normal pressure flow patterns while nine presented a urodynamic pattern as described above for trigonocele

Cystometrograms revealed two cases of uninhibited detrusor contractions Clinically all had bulging anterior vaginal walls Symptoms were stress incontinence 13 urge incontinence 8 gynecological complaints 4 straining micturitions 2 and recurrent cystitis 2

DISCUSSION

Postero-inferior support of the bladder and vagina is exerted by the levator muscles This is clearly demonstrated by asking the patient with a posterior descent to contract the pelvic floor This contraction lifts the vagina and the bladder base to a normal position Tanagho & Smith (10) point out that this laxity of the pelvic floor influences the sphincteric function of the urethra and gives rise to stress incontinence However only 13 of 29 patients in our study complained of stress incontinence Tanagho & Smith maintained that the same laxity which causes the low lying bladder may instead cause a trigonocele uncomplicated stress incontinence as it restores the sphincteric mechanism Our findings are in agreement with suggestion that a typical trigonocele is rarely panied by stress incontinence If a patient having trigonocele is asked to contract the pelvic floor the herniation is not repositioned but merely compressed from behind

As can be seen from the illustrations the vagina is postero-inferiorly displaced in both posterior bladder descent and trigonocele but in the latter the bladder neck does not follow the vagina This creates a space into which the trigone herniates The bladder neck therefore to some extent must be retained in its original position Curtis *et al* (1) state that the medial part of the levator muscle the pubococcygeus muscle gives off visceral fibres to the urethra the vagina and the rectum Treahy & Pacey (11) describe the same structures and on this finding they base a correctional surgical technique a pubococcygeus sling behind the urethra Ingelman Sundberg (5) divides the two pubococcygeus muscles and unites them behind the bladder neck to form a sling *These anterior connections from the pubococcygeus muscle may be intact in trigonocele and may be partly responsible* for retaining the bladder neck Furthermore th

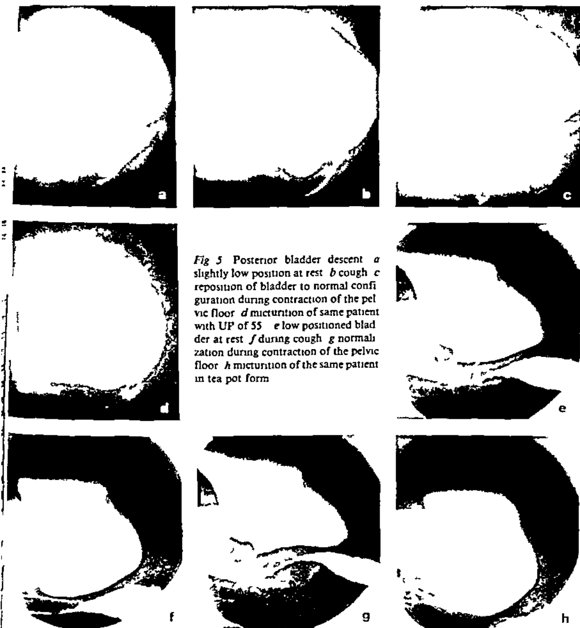


Fig 5 Posterior bladder descent *a* slightly low position at rest *b* cough *c* reposition of bladder to normal configuration during contraction of the pelvic floor *d* micturition of same patient with UP of 55 *e* low positioned bladder at rest *f* during cough *g* normalization during contraction of the pelvic floor *h* micturition of the same patient in tea pot form

strong fibro-elastic pubovesical ligaments dissected by Krantz (6) probably partake in keeping the bladder neck from sliding backwards

CONCLUSIONS

Radiologically trigonoceles may be divided into the following subgroups

1 The compensated form in which the detrusor contraction can lift the cele into a normal position resulting in norma micturition

2 The typical form with typical bladder neck outflow obstruction and corresponding urodynamics

3 The transitional form towards posterior bladder descent

4 The iatrogenic form detectable on high UP values

Trigonocele symptoms are mostly gynecological Stress incontinence is exceptional

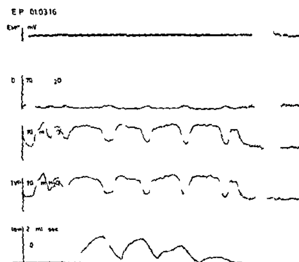


Fig 6 Posterior bladder descent Urodynamic examination

Posterior bladder descent radiologically has the following subgroups

1 Primarily low lying bladders that compensate to a normal position and normal micturition during detrusor contraction

2 Primarily low lying bladders that remain in the descended position during micturition These are associated with varied symptoms and varied urodynamic patterns

3 Primarily normally positioned bladders that descend during micturition the symptomatology being by stress incontinence Urodynamic patterns varied as with the preceding group

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SHORT COMMUNICATION

MEASUREMENTS ON THE HUMAN FETAL UTERUS AND OVARY

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Abstract Measurements of the growth rates of fetal endometrium myometrium and the fetal ovary between 13 to 36 weeks of gestation have been recorded The relationship of the measurements to the age of the fetuses are presented on the basis of a linear regression analysis It is concluded that the rates of growth are linear for the fetal uterus as well as the fetal ovary

The size of the ovary at term and that of the newborn and older child have been studied by various authors (1 2 3) It appears that a study of the thickness of the endometrium and myometrium and the size of the ovary during different stages of intrauterine life has not so far been carried out The present work was designed to study the growth rates of the uterus and ovary The application of a statistical method can be used to predict the size of the ovary and the thickness of the endometrium and myometrium at any age of the fetus

MATERIAL AND METHODS

Forty five human fetuses (from 13 to 36 weeks) from twenty seven therapeutic abortions and eighteen stillbirths were taken for the present study The stillbirths were taken from cases of abruptio placenta prolonged labor and cord prolapse leading to fetal death The age of the fetuses were calculated from the date of the last menstrual period

The ovaries and uteri were taken out by laparotomy The length and breadth of the fresh ovaries were measured by vernier calliper of 0 01 least count The uteri were immediately put in ten per cent formol saline for 48 hours Paraffin blocks were prepared from the proximal one third of the fundus uteri because the distal two third of the fetal uterus is cervix Transverse sections of each uterus were made at 7 micra and stained by hematoxylin and eosin Three measurements from the thickest part of the endometrium and myometrium were taken and the mean values were recorded in millimeters by a Leitz Screw the micrometer eye piece under transmitted light

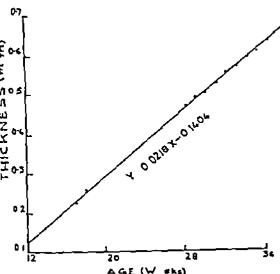


Fig 1 Scatter graph showing the thickness of the myometrium against the age of the fetus along with the fitted regression line

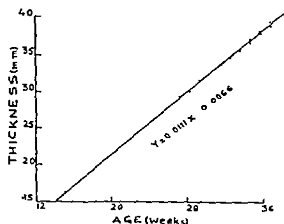


Fig 2 Scatter graph showing the thickness of the endometrium against the age of the fetus along with the fitted regression line

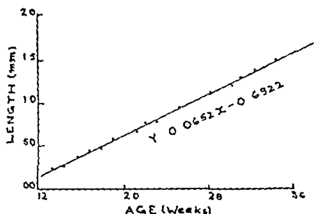


Fig 3 Scatter graph showing the breadth of the ovary against the age of the fetus along with the fitted regression line

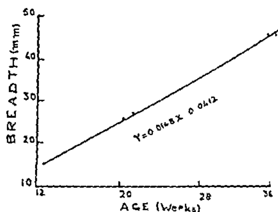


Fig 4 Scatter graph showing the breadth of the ovary against the age of the fetus along with the fitted regression line

RESULTS

The measurements of the thickness of the myometrium according to age are plotted in a scatter graph (Fig 1) along with the linear regression line Similar graphs along with the linear regression lines are also presented for the thickness of the endometrium the length of the ovaries and the width of the ovaries in figures 2 3 and 4 respectively

DISCUSSION

It is clear (Fig 1) that the thickness of the myometrium increases linearly with age and the regression coefficient of 0 0218 was found to be significant ($p<0\ 001$ $F\ (1\ 43)=47\ 64$) in accordance with the F test based on the analysis of variance The thickness of the endometrium was also found to increase linearly with age with a regression coefficient of 0 0111 which again was significant However the rate of growth of the myometrium was found to be much faster than the corresponding rate of growth of the endometrium

As for the ovary the length and width were both observed to increase linearly with age with regression coefficients 0 0652 and 0 0148 respectively which were statistically found to be significant

ACKNOWLEDGEMENT

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CASE REPORT

MONOAMNIOTIC TWINS DIAGNOSED BY ULTRASOUND IN THE FIRST TRIMESTER

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Abstract A case of monoamniotic twins was diagnosed by ultrasonic scanning in the first trimester through the presence of two fetuses in one gestation sac The fetuses died in utero in weeks 17 and 25 The possible ultrasound appearance of the various types of monozygotic and of dizygotic twins in early pregnancy is discussed and a scheme is suggested which allows some differentation

It is well established that fetal life can be reliably diagnosed at ultrasonic scanning as early as a menstrual age of 7 weeks (5) When the gestation sac has been demonstrated the fetus is located within the sac and the rhytmically moving echoes from the pulsating fetal heart are registered Since fetal size in early twin pregnancy does not differ from that of singleton pregnancies (2) twin pregnancy should also be diagnosable ultrasonically from the 8th week as two gestation sacs each containing a fetus Although this logical assumption seems to hold true in practical work there are at present no series in the literature to prove it Conversely we have encountered an exception to this rule which we describe here A case of *monoamniotic twins was diagnosed by ultrasound in* the first trimester through the presence of two fetuses in one gestation sac Furthermore we shall discuss the possible ultrasound appearance in early pregnancy of the different types of monozygotic and of dizygotic twins

CASE REPORT

A 25 year old woman gravida 2 para 2 with diabetes mellitus since the childhood was routinely referred to the ultrasound laboratory The first ultrasound examination in the 10th week showed a gestation sac containing a live fetus with a crown rump length of 31 mm corresponding to 9 to 10 weeks The next ultrasound examination in week 11 again showed a fetus with a crown rump length (41 mm) corresponding to the menstrual history but close to the fetal body we saw a rounded structure 1 5 cm in diameter which changed position in relation to the fetus and had pulsating inner echoes (Fig 1) A repeat examination the following day gave the same result and a malformed fetus maybe a monster was suspected

Finally the fourth scanning in the 13th week gave the correct diagnosis two separate fetuses in one cavity The scanning failed to disclose any membrane between the two fetuses and since the previous ultrasound examinations had shown only one gestational sac a diagnosis of monoamniotic twins was made Fetal growth was normal until week 17 when one fetus died The other one continued to grow at a normal rate until week 25 when this fetus also died Abortion was induced by intraamnial injection of prostaglandin Two female abortions were delivered A 550 grams 41 cm long and B 130 grams 30 cm long They were lying in one



Fig 1 Transverse scan 11 weeks gestation showing head of fetus (h) body of fetus (b) and round structure (?) with pulsating inner echoes in retrospect transverse section of second fetus

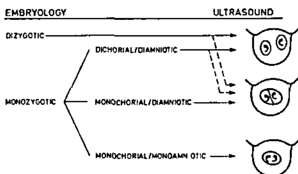


Fig 2 Scheme showing the expected relation between embryology and ultrasound findings in early twin pregnancy For details see text

amniotic cavity and had a common placenta The fetus B had its very thin umbilical cord twisted around the umbilical cord of the fetus A approximately 10 cm from its insertion into the placenta An autopsy showed no congenital anomalies

DISCUSSION

Monozygote twins result from the fertilization of a single ovum whereas in dizygote twinning two ova are discharged and fertilized in a single ovulatory cycle Approximately one quarter of all human twins monozygotic Depending on how early the sepa on takes place one of three different types of monozygotic twins develops (1 3)

1 Separation of the early blastomers results in twins which would start their intrauterine career just as if they were a pair of double ovum twins They will implant separately and will each develop its own placenta and membranes i e they will be dichorial diamniotic twins (25 – 30 per cent) At birth the obstetrician would have no means of knowing that they had come from a single egg cell

2 Duplication of the inner cell mass results in twin embryos which will be enclosed in a single chorion In addition the placenta is common but each embryo has its own amnion i e they are monochorial diamniotic twins (70 – 75 per cent)

3 Duplication of the embryonic rudiment of the germ disc results in twin embryos lying in one amniotic cavity with a common chorion and placenta i e they are monochorial monoamniotic twins (1 per cent) In some of these the separation is incomplete and gives rise to Siamese modifications

In the second and third trimester monoamniotic twinning may be suggested when scanning fails to disclose a membrane between the two fetuses Proof cannot be obtained since the membrane may be impossible to visualize with present ultrasound technology

We were able to diagnose definitely monoamniotic twins in the first trimester To our knowledge it is the first time this diagnosis has been made by ultrasound It encouraged us to consider the possible ultrasound findings in early twin pregnancy In weeks 5 to 7 when the gestational sacs occupy only a minute part of the uterine cavity three different ultrasound pictures could be expected (Fig 2) A two clearly separated gestational sacs with a fetus in each would be expected in most dizygotic and dichorial diamniotic twins B two gestational sacs with a common wall and with a fetus in each would be expected in monochorial diamniotic twins and by chance sometimes in dizygotic and dichorial diamniotic twins C one gestational sac with two fetuses would be expected only in monoamniotic twins Clinical evaluation of this theoretical scheme will have to wait until a series of ultrasound examinations in very early twin pregnancy is available

In monoamniotic twinning the risk of fetal death prenatally or during labor is very high with a fetal loss of 40 per cent (6) to some extend due to intrauterine death after the 36th week (4) A majority of the fetal deaths is associated with twisting and entanglement of the umbilical cords When the condition is kept in mind monoamniotic twinning should be diagnosable ultrasonically from the 8th week like other types of twinning The additional information on the exact type allows an adequate choice of the manner and time of delivery (possible preterm) and also suggests the potential of ultrasound in human embryology

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CASE REPORT

MATERNAL PULMONARY EDEMA OCCURRING AFTER THERAPY WITH RITODRINE FOR PREMATURE UTERINE CONTRACTIONS

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Abstract Intravenous administration of beta sympathomimetic drugs in combination with betamethasone or dexamethasone is a treatment often used for the suppression of premature uterine contractions and for the stimulations of fetal lung maturity It has been suggested that the combination of these drugs may be responsible for maternal pulmonary edema and five such cases have been reported in the literature (1 2)

We report a patient who developed pulmonary edema during ritodrine therapy Corticosteroids were not given in this case

CASE REPORT

A 18 year old gravida II para 0 woman was admitted 33 weeks after her last menstrual period with typical signs of left renal colic

The patient was treated symptomatically and two hours after admission her pain gradually ceased Three hours later regular uterine contractions were demonstrated by external monitoring and intravenous administration of ritodrine through an IVAC pump was started (0 1 mg/min)

The patient received the intravenous treatment for 12 hours (total fluids infused 700 cc total ritodrine 150 mg)

The contractions stopped and the patient continued to receive ritodrine orally 10 mg every 3 hours

24 hours after the beginning of treatment the patient developed dyspnea tachycardia and on auscultation typical signs of gross pulmonary edema were heard A chest roentgen ray film revealed pulmonary edema Digoxin and diuretic treatment were immediately started and over the next few hours all the symptoms disappeared

The next day the patient was asymptomatic and the roentgen ray chest film was normal

Phonocardiographic cardiac ultrasonography and the E.C G were normal ruling out hear disease

A few days later the patient was discharged in good condition without further treatment since the contractions had completely stopped and she was asymptomatic Four weeks later the patient delivered spontaneously a male infant of 3 100 grams with an Apgar score of 10 The post partum course was normal

COMMENT

From the few cases reported in the literature we learn that a beta sympathomimetic drug (terbutaline has been particularly implicated) in combination with steroids can induce pulmonary edema especially when given to a patient with an underlying cardiac disease

Our case shows that this combination of drugs and/or a previous cardiac disease are not a sine qua non for the development of pulmonary edema Even in a healthy pregnant woman particularly at 32–33 weeks of gestation when the plasma volume and cardiac output are maximally increased the beta sympathomimetic drug alone can induce pulmonary edema

We suggest that beta sympatomimetic drugs should not be given to stop premature labor in a pregnant woman with cardiac disease

Every pregnant woman receiving beta sympathomimetic drugs alone or in combination with steroids should be screened for cardiac disease before treatment and carefully watched during the treatment

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ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1981

Date	Place	Name	Office
1981			
January 26–31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Congr Admin 31600 West Chicago Livonia MI 48150 USA
March 14–18	Atlanta USA	37th Annual Meeting of the American Fertility Society	The American Fertility Society 1608 13th Avenue South Suite 101 Birmingham Alabama 35205 USA
March 22–26	Berlin West Germany	IIIrd World Congress of Human Reproduction	Dozent L Mettler Frauenklin der Univ Hegewischstr 4 D 2300 Kiel 1
March 27–28	Modena Italy	Symposium on Recent Advances on Pathophysiology of Amniotic Fluid	Scientific Secretariat Dr G C Di Renzo Istituto di Clinica Ostetricia e Ginecologica Policlinico Via del Pozzo 71 41100 Modena Italy
April 15–17	Gorizia Italy	International Course on Ultrasound in Obstetrics	Filippo Destro Organising Secretary Dept of Obstetrics and Gynecology City Hospital Via Vittorio Veneto 171 34170 Gorizia Italy
May 17–24	Dubrovnik Yugoslavia	4th European Congress on Ultrasonics in Medicine	Professor Asim Kurjak Ljubinkovac Stube 41000 Zagreb Yugoslavia
June 9–12	Ostend Belgium	Third International Congress on the Menopause	The International Menopause Society 8 av Don Bosco 1150 Brussels Belgium
June 22–26	Jerusalem Israel	5th World Congress of Medical Sexology	Secretariat P O Box 16271 Tel Aviv Israel
Jun–Jul 28–3	Tel Aviv Israel	2nd International Congress of Andrology	Secretariat P O Box 16271 Tel Aviv Israel
y 1–4	Graz Austria	First International Symposium on Minimal Invasive Cancer (Microcarcinoma)	Secretariat First Symposium on Minimal Invasive Cancer P O Box 105 A–1014 Wien Austria
August 20–	Nyborg Fyn Denmark	8th Nordic Congress on Perinatology	Dr Bo Lindberg Dep OB/GYN University Hospital S–75014 Uppsala Sweden
August 24–28	Cambridge England	XIII Acta Endocrinologica Congress	Conference Services Ltd XIII Acta Endocrinologica Congress 3 Bute Street London SW7 3EY England
September 13–16	Nijmegen Holland	International Symposium on Scanning Electronic Microscopy (SEM) of the Reproductive System	Symposium Secretary Gerda Theunissen Department of Obstetrics and Gynecology Sint Radboud Hospital University of Nijmegen 6500 HB Nijmegen the Netherlands
Sept-Oct 28–1	Venice Italy	13th International Meeting Organisation Gestosis	Centro Italiano Congressi Via L. Spallanzani 11 00161 Roma Italy
Sept-Oct	Athens Greece	VIth European Congress on Sterility (ESCO)	Sekretariat Prof Dr K Semm Frauenklinik der Universität Kiel Hegewischstrasse 4 2300 Kiel 1 West Germany
October 7–10	Paris France	Third practical course in colposcopy and cervicovaginal histopathology—in English	Dr Cartier L Enseignement Complémentaire en Gynécologie 20 Rue des Cordelieres 75013 France

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CASE REPORT

ACUTE SPONTANEOUS PUERPERAL INVERSION OF THE UTERUS

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Abstract Acute inversion of the uterus is a very uncommon but potentially fatal obstetric complication A case of acute spontaneous puerperal inversion is presented together with a survey of data concerning this obstetric emergency

The complicating condition of uterine inversion that is the uterus being turned inside out is dramatic serious and so rare that very few physicians are familiar with it Having experienced the drama of this unexpected emergency we feel the need to give a short review of the subject

Its reported incidence varies greatly from 1 5 000 to 1 250 000 deliveries (1 2 3) The figures obviously relate to the different standards of general obstetric practice as most of these cases are due to improper handling of the third stage of labor Traction of the umbilical cord when delivery of the placenta is delayed the repeated use of oxytocic drugs when the cervix is very relaxed fundal pressure in the abscence of uterine contraction uterine tumors and thinning of the myometrium at the site of fundal implantation of the placenta are etiologic factors Although doubted by some (3) spontaneous inversion of the uterus has been reported and does occur It is believed to be due to some abnormality of the uterine musculature and innervation

Inversion of the uterus is said to be complete when the fundus uteri protrudes through the cervix and into the vagina Often the entire uterus hangs outside the vulva The condition usually develops rapidly and is associated with hemorrhage pain and shock The amount of hemorrhage depends on the contractility of the uterus and on the completeness with which the placenta has separated The degree of shock often appears to be out of all proportion to the amount of bleeding due to stretching of peritoneal nerves and the broad ligament as these structures are often together with tubes and ovaries pulled into the funnel formed by the inverted uterus Successful treatment depends on the speed of recognition and institution of therapy If shock and blood loss are not predominant the person present at the time occurrence should initiate immediate reposition

If reposition of the uterus can be accomplished at this stage shock can be prevented Early replacement has the advantage that reposition can be accomplished by manipulation before the cervix becomes constricted and grips tightly the encircled portion of the inverted uterus thus interfering with repositioning and making surgery necessary If immediate replacement is not possible treatment of shock and hemorrhage as well as adequate anesthesia with good relaxation are essential before manual correction is started The placenta if attached is removed and the uterus replaced vaginally by careful manipulation

In patients where a cervical ring has developed the uterus then becoming congested and edematous it may be quite impossible to accomplish reposition manually and operation becomes necessary for a successful replacement Vaginal surgical procedures described by Spinelli and Küstner have been employed successfully the aim of both operations being to incise the tight cervical ring (1 2) In the Spinelli operation the bladder is dissected from the anterior uterine wall and pushed out of the way before the cervical ring is divided anteriorly The inverted uterus is then replaced The Küstner procedure differs into that the cervical ring is divided posteriorly Kirkley recommends vaginal supracervical hysterectomy as a time saving procedure (3) Operation by the abdominal route described by Huntington is another alternative (2) The uterus is grasped with Allis forceps about 2 cm below the ring and replaced by steady upward traction under direct vision

CASE REPORT

25 years old para I gravida II Her first delivery 3 years earlier was complicated by atonic intra partum bleeding puerperal bleeding due to retention of the placenta Th

tual delivery at term was spontaneous 5 1 E Oxytocin was given i m immediately after delivery 35 minutes after delivery the uterus was found to be totally inverted hanging outside the vulva the placenta still attached to the fundal region Prior to this the patient had complained of pressure towards the perineum and rectum Immediate reposition was not tried Instead the patient was given general anesthesia and about 10 minutes after discovery of the inversion a placenta accreta was removed (histologically verified) and manual repositioning was attempted However the uterus had becom edematous and replacement proved impossible through the firmly constricted cervical ring Bleeding was profuse the patient shocked blood pressurer 40/0 and surgical treatment became mandatory The cervical ring was cut anteriorly ad modum Spinelli and the inverted uterus replaced As hemorrhage continued and the uterus remained atonic in spite of oxytocic infusion an abdominal supracervical hysterectomy was performed Antibiotic coverage was given The postoperative course was uneventful mother and child were discharged from the hospital on the 8th day

DISCUSSION

As no fundal pressure or excessive cord traction had been exerted one must assume that this acute inversion of the uterus occurred spontaneously, most probably due to the fundal implantation of a placenta accreta Her atonic intra partum bleeding and retained placenta three years earlier and associated curettage might also be predisposing factors Prior to the discovery of the inverted uterus the patient had in fact complained of downward pressure and pain If a vaginal examination had been done at this point the diagnosis might have been established and the treatment initiated at an earlier stage Immediate manual replacement was not tried and ten minutes later manual reposition had become impossible as the cervical ring had already formed Thus it seems that a successful outcome in the management of patients with acute puerperal inversion of the uterus not only depends on correct methods of management but also on early recognition of the problem and prompt institution of therapy

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CASE REPORT

SPONTANEOUS RUPTURE OF THE LIVER IN PREGNANCY

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Abstract A case of spontaneous rupture of the liver in pregnancy fatal to mother and child is described The patient a multiparous 36-year-old diabetic presented in the 27th week of pregnancy with upper abdominal pains resembling biliary dyskinesia After 8 hours observation in the hospital she suddenly developed hypovolaemic shock and fetal heart tones disappeared On acute cesarean section a dead fetus was delivered Hemoperiteoneum was present arising from a huge subcapsular hematoma of the right lobe of the liver with rupture of Glisson s capsule The hematoma was evacuated and tears in the liver parenchyma sutured Disseminated intravasal coagulation complicated the early postoperative cause A bacterial infection supervened later and the patient died in a septic stage on the 19th postoperative day The literature is reviewed and it is pointed out that greater awareness of the diagnosis could lead to better timing of surgery and an improved prognosis for mother and child

Spontaneous rupture of the liver although rare is one of the gravest complications of pregnancy with maternal mortality in 59 per cent and fetal mortality in 62 per cent (3) Bis *et al* (3) recently reviewed the 91 cases known from the literature They found that the majority had occurred in multiparas in the third trimester and nearly all (85 out of 91 cases) had signs of pre-eclampsia The true incidence of the condition is unknown but reported figures vary from 1 case in 40 000 deliveries (7) to 1 in 250 000 (6) In nearly all reported cases the patient is observed in hospital for hours to days with undiagnosed abdominal pain whereupon her condition deteriorates with more severe pain and shock Emergency laparotomy then yields the correct diagnosis

The present case which is believed to be the first reported from Scandinavia followed this characteristic course

CASE REPORT

The patient was 36 years of age In 1961 a cholecystectomy had been done after 2 years of recurrent gallstone colics She was then healthy until April 1977 when diabetes mellitus was diagnosed this was well regulated by two insulin injections per day

Obstetric history IV para with normal deliveries in 1961 1964 1966 and 1967 These four pregnancies had all been uncomplicated In particular there was no record of preeclampsia

The present pregnancy Throughout the pregnancy the patient was followed regularly by an internist and the diabetes was well under control There were no unusual findings until the 26th week of pregnancy when a slight tibial edema and a blood pressure (BP) of 145/95 mm Hg were recorded and controlled with a thiazide diuretic and rest A week later the patient came to the obstetric outpatient clinic complaining of pain in the epigastric area irradiating through to the back No history or signs of physical trauma Examination showed slight tenderness in the right hypochondrium No other abnormalities With a tentative diagnosis of biliary dyskinesia symptomatic treatment with spasmolytics was prescribed Late in the evening the same day she returned to the hospital because the upper abdominal pains had increased On examination she was found to be pale and distressed with pain Abdomen diffusely tender but without rebound tenderness Uterus soft audible fetal heart sounds No vaginal bleeding BP dropped for a short while to 80 mm Hg systolic but returned to normal in response to an i v drop with Macrodex The patient was transferred to the obstetric department and observed here for the next 8 hours during which time her condition deteriorated hemoglobin dropping from 130 to 78 g/l Acute laparotomy was decided with a preoperative diagnosis of total ablation of placenta Just prior to operation the fetal heart sounds disappeared so a cesarean section was done A dead fetus was delivered The amniotic fluid was clear and the placenta normal The peritoneal cavity was explored and found to contain 1 5 l of dark blood The right lobe of the liver was greatly enlarged A tear laterally in Glisson s capsule was considered to account for the hemoperitoneum The left lobe and the other abdominal organs were normal As no fresh bleeding was seen it was decided to just insert drainage to the affected area and the abdominal wall was closed However shortly after the operation fresh bleeding started from the abdominal drains BP and central venous pressure dropped in spite of blood t ansfusions A new laparotomy was decided and ...un two and a half hours after the first operation The incision was extended to the xiphoid process and revealed that the dome of the right liver lobe was completely covered with a huge subcapsular hematoma 2 cm thick Glisson s capsule was torn laterally and medially close to the fal

ciform ligament Fresh bleeding oozed from the tears The hematoma was evacuated and the denuded surface of the liver presented multiple small tears The liver parenchyma required some hemostatic sutures Drainage was arranged and the abdominal wall closed During the two operations BP dropped to 50–60 systolic for periods of 10–15 minutes A total of 7 5 l of blood were given during the operations

The postoperative course was complicated Disseminated intravasal coagulation syndrome was suspected on the second postoperative day because of bleeding from the abdominal drains thrombocytopenia to 15×10^9/l (normal $180-350 \times 10^9$/l) blood concentration of fibrinogen degradation products above 40 mg/l oligouria and respiratory insufficiency Treatment with transfusions of fresh blood respirator heparin chlorpromazine and diuretics produced a slow improvement until the 11th postoperative day when a bacterial infection supervened Despite antibiotic treatment the patient gradually entered a septic state with unconsciousness paralytic ileus oligouria and high fever She died on the 19th postoperative day

Post mortem examination revealed a 2 810 g liver Glisson s capsule had been lifted off the parenchyma over an area 8 × 8 cm on the anterior aspect of the right lobe The underlying parenchyma had multiple small tears Microscopic examination of the liver revealed zones of cell necrosis Fibrin thrombi were found in the small periportal vessels The kidneys showed tubular necrosis and here too intravascular fibrin thrombi were seen In the lungs there were hyaline membranes in the alveoles and fibrin thrombi in the small vessels The cause of death was concluded to be disseminated intravascular coagulation combined with hyaline membranes in the lungs and renal tubular necrosis (Signed Kerstin Boström)

DISCUSSION

Rupture of the liver without significant trauma has been known as an obstetric complication since 1844 when Abercrombie (1) reported a case from Cape Town From time to time since then reports have appeared from all over the world The exact etiology is unknown but it is commonly agreed that presence of pre eclampsia leading to vascular damage of the liver is a main factor The existence of fibrin thrombi in the liver in many of these cases supports the view that disseminated intravascular coagulation may occur in pre eclampsia Normally intravascular fibrin is removed by two mechanisms fibrinolysis and phagocytosis by the reticuloendothelial system (RES) However potent activators of fibrinolysis are lacking in the liver and placenta (11) If the RES in the liver is blocked deposits of fibrin in the hepatic arterioles fanning out into the periportal sinusoids would lead to focal hepatic necrosis This combined with an abnormal coagulation profile could be followed hematoma formation perhaps precipitated by minor traumas unrecognized by the patient (3) One h thesis (10) is that pregnancy may sensitize the RES thereby preventing phagocytosis in subsequent pregnancies This might explain why spontaneous hepatic rupture has been observed mostly in multiparas when primiparas have the higher incidence of pre eclampsia That diabetes mellitus may play a role is suggested by 7 patients reported by Hibbard (6) of whom one was a diabetic and two others had clinical evidence suggesting latent diabetes Apart from a diseased liver most authors believe that minor traumas which a normal liver would ordinarily withstand might precipitate the formation of a subcapsular hematoma and capsular rupture

The present case is a good example of the rather characteristic course of events in this entity as described in most reports The patient usually presents with severe constant pain in the epigastrium and/or the right hypochondrium Physical examination reveals upper abdominal tenderness in a few cases also hepatomegalia but most often at this stage the correct diagnosis is missed and biliary colic (as in this case and many others) pancreatitis (12) and myocardial infarction (5) are usually considered In a few cases liver scans have contributed to a correct preoperative diagnosis (4) but otherwise the laboratory has provided little assistance In nearly every case the patient has been under observation in hospital when—hours to days after the onset of symptoms—signs of hemoperitoneum and hypovolemic shock develop as Glisson s capsule ruptures Even at this stage the exact diagnosis is nearly always missed and the most frequent preoperative diagnoses have been perforating gastric ulcer occult abruptio placentae or ruptured uterus Non-operative treatment has been fatal in all cases but one (6) Of 34 patients who underwnet laparotomy 22 survived giving a mortality of 35 per cent (3) In view of the high frequency of coagulopathy (8) it is recommended that blood for coagulation status should be obtained prior to surgery and massive transfusions For surgical treatment most authors recommend evacuation of the subcapsular hematoma and suturing of tears in the liver with a blunt needle with ligation of bleeding points In a few cases hepatic lobectomia has been carried out (9) Delivery of the infant by cesarean section at the time of laparotomy is recommended as continuation of the pregnancy has been shown to aggravate the prognosis for mother and child (2 13)

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W C G O

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CASE REPORT

CHRONIC GRANULOCYTIC LEUKEMIA IN PREGNANCY

A case report and review of the literature

Oded Shalev Samuel Heyman Giora Hod and Rahel Adato

From the Departments of Internal Medicine Surgery and Gynecology and the Hematological Service Hadassah University Hospital Mount Scopus Jerusalem Israel

Abstract Chronic granulocytic leukemia (CGL) was diagnosed in the second trimester of pregnancy in a mother of four who decided to terminate the pregnancy immediately According to the literature this unusual combination is not a definite indication for abortion since CGL does not adversely affect the course of the pregnancy nor the pregnancy alter the course of the disease Prudent treatment with busulfan or splenic irradiation when indicated apparently does not endanger the development of the fetus

The occurrence of leukemia during pregnancy has been known since the time of Virchow (12) Following his report in 1845 more than 150 cases have been described of which about half were suffering from CGL (3 4 6 9 10 13 14 15 18) The coincidence of the two conditions imposes unique therapeutic problems involving both mother and child We wish to report a case in which CGL was diagnosed during the second trimester of pregnancy to discuss the therapeutic alternatives and to review the literature

CASE REPORT

A 26 year old mother of four was referred to the Hematological Service during the fifth month of pregnancy because of a white blood count (WBC) of 5×10^9/L found on a routine blood examination Abnormal physical findings were confined to hepato-splenomegaly The size of the uterus was consistent with a pregnancy of twenty weeks Laboratory examinations disclosed a WBC of 83×10^9/L the differential of which was typical of CGL Hb 11 g/dl and platelets 250×10^9/L The morphology of the bone marrow aspirate and the presence of the Philadelphia chromosome in the karyotype confirmed the diagnosis of CGL After the patient was informed of the nature of her illness she requested that the present pregnancy be terminated and the possibility of future pregnancies be prevented We therefore decided to perform in one operation a therapeutic splenectomy termination of pregnancy (in accordance with the patient s wish) via cesarean section and tubal ligation No particular surgical problems were encountered during the operation The fetus was unremarkable Its bone marrow was normal for a five month fetus and its karyotype normal unlike that of its mother which was Philadelphia chromosome positive

During the operation the fetal liver which contains 80 per cent of the hematopoetic activity at this stage of gestation, was extracted and processed for cryopreservation

The predictable post splenectomy thrombocytosis of up to 750×10^9/L which developed after the operation was treated with 300 mg sulfinpyrazone per day until the surgical wound healed whereupon cytotoxic therapy with thioguanine and hydroxyurea was substituted This effectively controlled the CGL The patient has been maintained on thioguanine and hydroxyurea and her condition has remained hematologically stable over the past six months

DISCUSSION

Following the original description of leukemia during pregnancy in 1845 Sheehy (15) collected 89 cases of CGL occurring during pregnancy that had been reported up till 1958 In 66 of them the CGL had been diagnosed prior to the pregnancy and during pregnancy in the other 23 The next large series on the subject was reported by Moloney (10) who collected 69 cases of concurrent leukemia and pregnancy between 1958 and 1963 19 of the 22 women with CGL bore normal infants Ask Upmark (1) reported another 3 women with CGL who had normal pregnancies and whose infants were normal Still another patient was first found to have CGL during the seventh month of her pregnancy She received no treatment and the pregnancy terminated in the birth of a normal child (7) Fourteen months after the diagnosis she became pregnant again and this tim opted for a therapeutic abortion

The disease seems to have no deleterious effect on the offspring The child born to a mother suffering from CGL was followed for 20 years and found completely normal The CGL was diagnosed when the mother was in the first trimester of pregnancy and treated with splenic irradiation the pregnancy was terminated by cesarean section because of eclampsia (11) For a period of more than 30 years Bjure (2) followed the children and grandchildren of another patient with CGL again no trace of the disease was found Likewise pregnancy does not seem to change the natural course of CGL The median survival of 44 women with CGL who became pregnant during the course of their disease was 38 months (12) This mean is not significantly different from that of the rest of the the adult CGL population (17)

The current cytotoxic treatment available for CGL is a potential menace to the developing fetus (16) It is therefore recommended that therapy be withheld if possible at least until the end of the first trimester If howeve the patient develops signs of accelerated activity of the disease such as a very high WBC and massive splenomegaly specific anti leukemic therapy should be instituted Busulphan the classical drug for CGL (8) appears to be the safest drug under these circumstances The newborns of 12 women with CGL who were treated during their pregnancy with busulphan were all normal even though 10 of the mothers received the drug during the first trimester (9 13) Moloney s review (10) includes another 12 women who were treated with busulphan during the course of their pregnancy and in 6 of them this drug was the only therapy administered Only one of the women gave birth to a malformed child (5) Although busulphan was implicated in this case the patient also received 6-mercaptopurine and splenic irradiation in the first trimester Another cytotoxic drug dibromo mannitol was successfully used between the 10 – 17 weeks of a pregnant woman with CGL The child was normal at birth and remained so during the four year of follow up (3)

Although the experience with splenic irradiation is limited it appears to be a safe therapeutic alternative especially when the CGL is diagnosed early in the pregnancy and the uterus is still small enough to be shielded (14)

Our patient a mother of four children preferred to terminate the pregnancy The relatively advanced stage of the pregnancy her wish to prevent further pregnancies and our policy to perform therapeutic splenectomy in the early stages of CGL (19) dictated that all the surgical procedures be done in one operation abortion via hysterotomy tubal ligation splenectomy The post splenectomy was treated with the anti platelet agent sulfinpyrazone and as soon as the surgical wound had healed definitive therapy with the cytotoxic agents hydroxyurea and thioguanine was instituted

In summary CGL does not appear to affect adversely the course of the pregnancy nor the fetus Moreover there is no evidence that the pregnancy alters the natural course of the disease nor the mean survival in mothers with CGL In spite of the relative safety of the treatment of CGL it is recommended that it be deferred until at least the second trimester unless the mother s health is endangered by an otherwise uncontrolled activity of the disease The experience primarily with busulfan and splenic irradiation although limited is the best available to date

ACKNOWLEDGEMENT

The authors thank Professor E Rachmilevich for referring the patient and reviewing the manuscript

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ANNOUNCEMENT

The Pan American Congress of Andrology will take place in Mexico City Americana Fiesta Palace Hotel January 26–31 1981

Informations requests for registration and travel information should be directed to

Dr A Negro Vilar
University of Texas Health Science
Center at Dallas
Southwestern Medical School
Department of Physiology
5323 Harry Hines Boulevard
Dallas Texas 75235
USA

Informations requests for registration and travel information should be directed to

Gerald Bagazinski
Congress Administrator
31600 West Chicago
Livonia Michigan 48150
USA

The Third International Congress on the Menopause will be held in Belgium at the coastal resort of Ostend in June 9–12 1981 just before the holiday season begins

This Congress will differ from the previous two (in La Grande Motte 1976 and in Jerusalem 1978) in that where as the aim in the past was to arrive at a consensus of opinion this time we shall bravely attempt to confront the controversies It will however take the same form as the earlier ones — a number of small workshops rather than one large meeting attended by everyone

For further information

The International Menopause Society
8 av Don Bosco
B-1150 Brussels
Belgium
Tel (02) 771 95 98 and (02) 771 96 45

The IIIrd World Congress of Human Reproduction is to be held in West Berlin March 22 26 1981

Main topics

Central nervous system and regulation of reproduction
Surgical and morphological aspects of reproduction in men and women
Gonadotrophins and their target tissue
Beginning of life *in vivo* and *in vitro*
- Experimental embryology of mammals

High risk reproductive factors in breast and genital cancer
Influence of the environment and drugs on reproduction
Free Communications
- Film Festival

Information

Congress Secretariat
Priv Doz Dr L Mettler
Frauenklinik der Universität
Hegewischstrasse 4
D-2300 Kiel 1
West-Germany

An International Symposium on Scanning Electronic Microscopy (SEM) of the Reproductive System will be held in Nijmegen The Netherlands September 13–16 1981

The Symposium will consist of sessions (1) fundamentals of SEM preparations (2) reproduction morphology (3) reproductive pathology (4) advanced techniques and clinical application

Each will comprise invited lectures and free communications Keynote lectures will include Hans Ludwig Godfried Roomans Eva Patek James Koehler Kenneth Gould *Lourens Zaneveld a o*

Selected and extended abstracts will be published The deadline for submission of abstracts *is April 1 1981*

Further details may be obtained from

Symposium Secretary Gerda Theunissen
Department of Obstetrics and Gynecology
Sint Radboud Hospital
University of Nijmegen
6500 HB Nijmegen
the Netherlands
Phone 80-514725

Acta Obstet Gynecol Scand 59 567–569 1980

CASE REPORT

LIVER CELL CARCINOMA IN YOUNG WOMEN POSSIBLY INDUCED BY ORAL CONTRACEPTIVES

Flemming Amtrup Jørgen Slottved and Hans Svanholm

From the Institute of Pathology and the Department of Neurology Vejle Sygehus Denmark

Abstract Two cases of liver cell carcinoma in young women ingesting oral contraceptives have been found within a few months in the county of Vejle Denmark In luding these two patients 22 cases of liver cell carcinoma in young women have been published since 1973 19 of whom have used oral contraception The possible effects of oral con traceptives in inducing liver tumors is discussed and it is pointed out that no statisti al proof of such an effect exists at present

Primary hepatic cancer is a relatively frequent disease in Asia and Africa (2 21) but is uncommon in western countries It is most often seen in the middle aged and in men (28)

However in Denmark the incidence of primary hepatic cancer exclusive of sarcoma has varied from 4 to 5 0 per 100000 age adjusted European standard population per year among men from 1943 to 1972 and among women the corresponding figures are 2 9 to 6 3 the latter incidence being for the period 1943–1947 (8) Liver cell carcinoma is frequently combined with cirrhosis of the liver the recorded incidence varying from 17 per cent to 70 per cent (12 21)

During recent years a possible connection between oral contraception and liver cell carcinoma has been discussed A connection between liver cell adenoma or focal nodular hyperplasia and oral contraception was postulated by Kay and Shatzki 1971 (19) Hovath Kovacs and Ross 1972 (17) and by Baum Bookstein Holtz and Klein (1973 (3) In September 1976 117 such cases were published and 120 additional cases mentioned (but not proved) in the literature or 237 cases in all (20) The diagnosis were liver cell adenoma (3 9 11) one hepatoblastoma (23) focal nodular hyperplasia (24 30) and possibly one hamartoma (26)

Since 1975 several cases of liver cell carcinoma in young women taking oral contraceptives have been published (5 13 14 15 16 20 22 32) a total of 20 cases up till July 1978 (7) Among these women 17 had taken oral contraceptives for from 6 to 120 months and all the cases have been without cirrhosis (7 20)

CASE REPORT

Case 1 A 22 year old previously healthy woman was admitted to hospital in July 1978 16 months post partum because of gastroenteritis which had lasted 10 days She developed an encephalitis-like disease and died
Sterile autopsy In the right lobe of the liver a tumor with a greatest diameter of 15 cm was found No virus was cultivated Presumptive cause of death was hepatic coma
Microscopy of the tumor Liver cell carcinoma No cirrhosis
Gynecology During her sixteenth and seventeenth years she had used oral contraceptives containing both estrogen and gestagen name unknown Normal delivery March 1977 She had used Mini Pe (0 3 mg norethisteronum daily) before the delivery and six months after

Case 2 A 20 year old previously healthy woman was admitted to hospital in October 1978 six months post partum because of a wish for abortus provocatus and because of pain in the epigastrium in which region a palpable tumor was found After ultrasonic scanning a solid tumor in the liver was suspected At laparotomy a tumor with a greatest diameter of 9 cm was found in he left lobe of the liver and hemi hepatectomia sinistra was carried out No postoperative complications
Microscopy of the tumor Liver cell carcinoma No cirrhosis
Gynecology Menarche 197? From February 1975 to February 1977 she had used oral contraception (Ovanone 7 tablets with 50 microgram ethinylestradiolum 15 with 2 5 mg lynestrenolum and 50 microgram tradiolum) Normal deli ery April 1978

DISCUSSION

Since the beginning of this decennium the number of liver cell adenomas and focal nodular hyperplasias published in the literature from several western countries has increased dramatically

It has been suggested that liver cell adenoma and focal nodular hyperplasia represent two phases of the same disease which may develop into liver cell carcinoma (10 20)

There has been an increasing interest in sex steroids and contraceptives as a possible cause of liver tumors (3 4 5 6 7 9 10 11 13 14 15 18 20, 22 23 24) It is well known that sex steroids and oral contraceptives change the ultrastructural picture and function of the liver (1 29)

It has been stressed that women who use oral contraceptives may show dilatation of the periportal sinusoids which may look like peliosis hepatis (33) The same change has been described in many of the cases published in which young women ingesting oral contraceptives have developed hepatic tumors (9 10 13 24) and in our case 1 dilatation of sinusoids and small veins was found

In both our cases the intake of oral contraceptives was of short duration patient 2 using Ovanone for only 2 years while patient 1 had used an unknown contraceptive of the usual combination type for only 1 – 2 years and after that used a gestagen pill for six months before and six months after her pregnancy It is remarkable that both the tumors were diagnosed post partum and in case 2 furthermore in early pregnancy Previously hepatic tumors have been found in connection with pregnancy or the puerperium among women not using oral contraceptives (4 6) One more case of liver cell carcinoma found during pregnancy has been published but previous to her pregnancy this patient had received longterm treatment with estrogen like tablets (31) In our case 2 we found deposits of alpha 1 antitrypsin in the tumor cells which Palmer *et al* also found in 8 out of 9 of their cases of malignant hepatoma

According to the Danish Cancer Registry the number of malignant hepatic tumors exclusive of sarcomas in men and women has not increased from 1943 to 1972 the last half of the period coinciding with the general use of oral contraception among women (8)

According to Christopherson and Mays the National Cancer Institute has calculated that about 35 million women in USA have used or do use oral contraceptives (6) Since 1973 22 cases of liver cell carcinoma of young women including our two cases are on record Of these cases 19 have used oral contraceptives The risk of contracting liver cell carcinoma by using oral contraceptives The risk of contracting liver cell carcinoma by using oral contraception must therefore be extremely small if there is any connection at all Previous to the general use of oral contraceptives liver cell carcinomas occasionally were found in young people also in women How important oral contraceptives are among presumably many other pathogenic factors is still unknown There is still no statistical evidence that oral contraceptives are causative

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LETTER TO THE EDITOR

PERINATAL ASPHYXIA IN SPITE OF A NORMAL CARDIOTOCOGRAM AND A NORMAL ACID BASE STATE AT THE TIME OF DELIVERY

Dear Sir

In the case described by Dr T Weber (Acta Obstet Gynecol Scand 59 371 – 373 1980) the cardiotocogram is said to be essentially normal

Except for the initial 14 minutes (Fig 1) and the last 25 minutes (Fig 3) the FHR baseline shows in my opinion a rather pronounced silent pattern which in this case should arouse suspicion of acidosis corroborated by the depressed HPL values The FHR variations related to contractions described as early decelerations show on 8 occasions initial and/or terminal accelerations raising a suspicion of umbilical cord pathology

The neonatal depression of the newborn might have been caused by placental insufficiency (low HPL silent pattern) and pathological umbilical cord circulation (variable decelerations)

Against this background the statement Noinfections anomalies or other explanations for the perinatal depression were found is too cursory Was the case really scrutinized for any pathology regarding the umbilical circulation? Was the placenta investigated histologically?

October 27 1980

Helge Jenssen

Submitted for publication October 27 1980

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LETTER TO THE EDITOR

Dear Sir

In a recent issue (59 371) of Acta Obstetricia et Gynecologia Scandinavica author T Weber presents a case of perinatal asphyxia in association with normal cardiotocogram

Since the interpretation of the cardiotocogram during the second stage of labor is essentially different from our clinical practice I wish to make some remarks on decelerations Dr Weber regards the decelerations (varying in size and shape!) as early decelerations—which should be uniform (as in Fig 1) According to our concept the decelerations in the second stage are typical variable decelerations indicating an umbilical compression which also explains the low Apgar score at one minute The rapid recovery of the newborn accords with this concept I hope that readers of the journal will benefit from this comment as an example of the difficulties encountered when making a visual interpretation of cardiotocograms

Yours sincerely
V Kariniemi

Submitted for publication

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LETTER TO THE EDITOR

In reply to the letters of Drs Kariniemi and Jenssen regarding my paper in Acta Obstetricia et Gynecologica Scandinavica (59 371 1980) I have the following comments concerning the cardiotocogram (CTG) of the second stage of labor (Fig 3)

1) Although the decelerations during the short (10 min) second stage of labor might be interpreted as variable decelerations they are in principle early decelerations (caused by head compression) as each bearing down-effort is seen together with a drop in the fetal heart rate (FHR) This drop is the more pronounced the higher the intrauterine pressure is during the bearing-down-effort
2) Umbilical cord compression causes respiratory acidosis with acute accumulation of CO_2 and an increase in the A V difference in pH and pO_2 of the blood of the umbilical cord vessels (3) The acid base parameters in the discussed case thus did not indicate cord compression as pCO_2 of the umbilical artery and vein was normal (7 5 and 6 1 respectively) and as the A V difference in pH and pO_2 of the umbilical cord vessels were normal (0 07 units and 1 4 kP respectively)
3) Even if the second stage decelerations are called variable they are mild variable decelerations (decrease in FHR less than 60 beats per minute) (1) Consequently the low Apgar score in the present case cannot be explained by the decelerations as mild variable decelerations during the second stage of labor are not associated with low Apgar scores (1)
4) No abnormal position of the umbilical cord was found at delivery the length of the umbilical cord was normal and the placenta was normal although not investigated histologically

Concerning the CTG during the first stage of labor (Figs 1 and 2) I have the following comments

1) The variability was normal [never less than six in frequency (oscillations per min) and amplitude (beats per min)] (2)
2) Although it is a matter of debate whether the decelerations during the first stage of labor are variable or early they are mild moderate and never severe (2) According to Krebs *et al* (2) the CTG should thus be described as uncomplicated with mild moderate variable decelerations a pattern not related to low Apgar scores one (and five) minutes after delivery
3) The CTG did not change after tissue pH had reached normal values

In conclusion this discussion demonstrates the difficulties in interpreting a cardiotocogram In my opinion this problem can only be solved when tissue pH monitoring can be performed during all CTG monitored deliveries

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